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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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LOBAR PNEUMONIA AND DIGITALIS. By ALFRED E. COHN, M.D., and WILLIAM H. LEWIS, JR., M.D. 457

PNEUMONIA IN UNDULANT FEVER. A REPORT OF THREE CASES. By RICHARD M. JOHNSON, M.D. 483

VALUE OF SERIAL ELECTROCARDIOGRAMS IN CORONARY THROMBOSIS. By HARRY A. RICHTER, M.D. 487

OBSERVATIONS ON THE EFFECT OF AN ARTERIOVENOUS FISTULA ON THE HUMAN CIRCULATION. By L. B. LAPLACE, M.D. 497

STUDIES ON THE STRUCTURE AND FUNCTION OF BONE MARROW. IV. BONE MARROW IN AGRANULOCYTOSIS. By R. P. CUSTER, M.D. 507

A STUDY OF THE DIAGNOSTIC VALUE OF STERNAL PUNCTURE IN CLINICAL HEMATOLOGY. By CARL REICH, M.D. 515

THE EFFECT OF ULTRAVIOLET RAYS ON SNAKE VENOMS. By DAVID I. MACHT, M.D., LL.B., PHAR.D., LITT.D., F.A.C.P. 520

EFFECTIVE TREATMENT OF ARACHNIDISM BY CALCIUM SALTS. A PRELIMINARY REPORT. By ELMER W. GILBERT, M.D., and CHARLES M. STEWART, M.D. . 532

HYPOPROTEINEMIC NEPHROSIS AND ITS TREATMENT WITH ACACIA. REPORT OF TWO "CURED" CASES. By JOSEPH H. BARACH, M.D., and D. HARTIN BOYD, M.D. 536

THE EFFECT OF EQUIVALENT AMOUNTS OF DEXTROSE AND STARCH ON GLYCEMIA AND GLYCOSURIA IN DIABETICS. By MAX WISHNOFSKY, M.D., and ARTHUR P. KANE, M.D. 545

DERMATITIS GANGRENOSA. A COMPLICATION OF DIABETES MELLITUS. By SAMUEL S. RIVEN, M.D., F.A.C.P. 550

TEMPERATURE DETERMINATIONS IN THE FEMALE PELVIS DURING DIATHERMY. By EDWARD A. HOROWITZ, M.D., DAVID DEROW, M.D., and WILLIAM BIERMAN, M.D. 555

ACUTE PRIMARY DIAPHRAGMITIS (HEDBLOM'S SYNDROME). By MINAS JOANNIDES, M.D., M.S., F.A.C.S. 566

VITAMIN A CONTENT OF HUMAN LIVER. By PAUL D. CRIMM, A.B., M.D., F.A.C.S., and DARWIN M. SHORT, A.B. 571

INDEX TO PHYSICIAN'S SUPPLIES . . . . . ADV. PAGE 38

Contents continued on adv. page 10

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1935

ORIGINAL ARTICLES.

LOBAR PNEUMONIA AND DIGITALIS.

By Alfred E. Cohn, M.D.,

and

William H. Lewis, Jr., M.D.,

new york.

(From the Hospital of the Rockefeller Institute for Medical Research.)

The question is still undecided whether the action of digitalis benefits patients suffering from lobar pneumonia. This question is, of course, distinct from the one which asks whether giving digitalis to such patients acts at all. To the second question, the evidence permits an affirmative answer.[1] In view of the value which giving digitalis may possess, a decision on the first question is eminently desirable. A solution has not been possible because a simple test is not available. Reliance must still be placed on its average behavior.

The careful and detailed study which was published by Wyckoff, DuBois and Woodruff[2] and by Niles and Wyckoff[3] has focussed attention anew on this problem. The plan of their study offered several advantages: (1) It dealt with relatively large numbers; (2) the duration of the observations was brief; (3) the dose and value of the preparation used was known; (4) an attempt was made, by strict alternation of cases, to solve the problem of control. To complete the investigation in a brief period has presumably this virtue, that the virulence of the infection may be regarded as having remained uniform. And strict alternation of patients has presumably this additional virtue that, provided the number of patients is large enough, the treated and the untreated include in adequate numbers all the varieties of resistance presented by patients. The

method of alternate selection appears to be the method of choice when the number of variable pathologic phenomena is large and their value difficult to assess. The method escapes the embarrassment due to these causes (number and value of phenomena) on the assumption that the cases become distributed equally in two great groups with reference to a selected variable, such as the effect of the action of digitalis. It is the familiar experiment of tossing a penny. The conclusion drawn from this study was "that the routine giving of digitalis to patients with lobar pneumonia is dangerous."[2]

The validity of the method for the purpose of studying the value of giving digitalis in cases of lobar pneumonia may be tested from two points of view; in the Bellevue study:[2,3] (1) Was the virulence of the infection constant, as was supposed to be the case during the brief duration (2 years) of the observation? and (2) Is the reaction of patients sufficiently alike so that they may be treated like the pennies in the experiment?

1. To be certain that the degree of virulence remained uniform is perhaps impossible. The data concerning mortality which are available show that in the Bellevue-Yorkville district (New York City), within which the Bellevue Hospital is situated, in the 5-year period, 1927–1931,[4] the death rate per 100,000 from pneumonia (all forms) varied from 126 (Area 112) to 340 (Area 64). The Bellevue Hospital is located in Area 60 and here the rate was 631. During the same period the rate in Bellevue-Yorkville district was 210; in Manhattan, 169; in New York City, 127. The inference which is drawn is that virulence, reflected in rates of mortality, so far at least as it can be judged by such methods, was not uniform.

2. Susceptibility also varies.[5,6] The risk may conceivably differ if, in patients, three lobes of the lungs are involved rather than one; if the age is over 40; if bacteria are present and persist in the blood; if complications are present; if patients are alcoholic; if they are hard manual workers. Niles and Wyckoff did, in fact, regard sex, age, type of pneumococcus, complications, bacteriemia and auricular flutter in their estimate of the effect of giving digitalis. But comparing treated and untreated cases from the point of view of these disadvantages, one at a time, fails to take into account the risk which a given individual runs. He is not of a certain age nor suffering, one at a time, from bacteriemia, from complications or cardiac arrhythmia. He is, as a matter of fact, a person whose chances of recovery may depend precisely on the variety and on the number of these or other untoward factors of which he is the subject. But judgment should be delayed until it is demonstrated that the issue depends on what might be called "the severity of the disease." Niles and Wyckoff take this consideration into account in 1 instance in which they combine two factors, age and type of pneumococcus (Table 6).[3]

Because of the difficulties involved in the method of alternating cases, the analysis now reported was undertaken from the point of view of the principle of "severity of disease."[5, 6, 7] At the basis of this principle is the idea that patients suffering from lobar pneumonia encounter risks far from uniform. The risk varies, presumably, with the kind and number of factors of an untoward nature which each case presents. These are being called "untoward," "unfavorable," "disadvantageous" factors or phenomena or elements. Eight such factors have been singled out for study. Still other ones might have been chosen.[5] Obviously from this point of view the analogue of the experiment with a two-sided penny requires extension. As many such experiments must be carried on as there are groups of patients. Since there were 146 groups in this series, an adequate number of patients would be very large even if the permissible error were 10%. Alternation of cases is unnecessary, since uniformity of virulence and of resistance may not be expected. This consideration suggests that hitherto an insufficient number of cases has been made to serve as the basis of a study in which the method of alternation is utilized.

TABLE 1.—LOBAR PNEUMONIA. PATIENTS IN THE HOSPITAL OF THE ROCKEFELLER INSTITUTE, FEBRUARY, 1911, TO JULY, 1932.

	Total patients.	Number recovered.	Number died.	Mortality, %.
Men	1063	862	201	18.9
Women	393	307	86	21.9
Total	1456	1169	287	19.7

Method. For the investigation now to be reported an analysis of the records of 1456 patients observed in the Hospital of the Rockefeller Institute has been undertaken (Table 1). The patients were treated during a period of 21 years, from 1911 (February) to 1932 (July). Theoretically the length of time may be regarded a disadvantage; practically this is not necessarily the case for a study of the fatalities throughout this period shows that the deviation from the average death rate, month by month, is $\pm 4.21\%$ and seems negligible. This result compares not unfavorably with that in the Bellevue-Yorkville district in the period when the investigation at the Bellevue Hospital was taking place. Carrying on a study of an infectious disease over a brief period may, in point of fact, present a disadvantage; the time selected may lie within a time of epidemic manifestation. If a longer view is to be taken, spreading the duration of observation may conceivably be an advantage.

I.

It was necessary first, as already suggested, to decide which "untoward" phases of lobar pneumonia should be singled out for analysis. Traditionally, being alcoholic, and being engaged in

hard labor, have been regarded as unfavorable factors with which to contend in the process of recovery. To the importance of pneumonia as a common cause of death in old age reference is not infrequently made. But there are other untoward factors beside age, alcoholism, and hard work. These have been analyzed each by itself. Those which, among others no doubt, have an influence on the outcome are apparently:

A. Type of work (Fig. 1).
B. Type of pneumococcus (Fig. 2).
C. Age (Fig. 3).
D. Alcoholism (Fig. 4).
E. Bacteriemia (Fig. 5).
F. Number of lobes involved (Fig. 6).
G. Cardiovascular affections (Fig. 7).
H. Complications (Fig. 8).*

Having done heavy work presents an added risk; so does infection with pneumococcus Types II and III†; age is distinctly a factor and is the more serious the higher the decade, the risk being 3 times greater after than before the age of 40; mild alcoholism is apparently of no consequence; the presence of bacteriemia quadruples the danger and its continued presence raises it about 8 times; involvement of more than two lobes of the lungs raises the risk from 24% (two lobes) to 41% (three lobes) and to 75% and 100% when four and five lobes, respectively, are involved; the complications which were encountered have varying significance, the important ones being empyema when not operated upon, pulmonary abscess, meningitis, pulmonary, renal and cardiac affections. In the sense that heavy work, infection with pneumococcus Types II and III, age over 40, more than moderate use of alcohol, bacteriemia, cardiovascular affections and certain complications have been regarded as factors having an unfavorable influence, so may lighter or less severe phases in each of these categories be grouped and the rates of mortality of patients affected by them be calculated. When this is done (Fig. 9) it appears that the rate is uniformly low—lower distinctly in each class than when the severer phase in that class is experienced.

Certain possible factors seem, on the other hand, to have had no importance in the outcome:

1. The number of previous attacks of pneumonia.
2. Serum sickness, after specific therapy with serum.

The influence of specific and other forms of therapy requires separate analysis. In this study they have not been taken into consideration. Nor has treatment with antipneumococcus serum

* These elements will be referred to occasionally by letter.

† Since this analysis deals with cases admitted to hospital before July 1, 1932, further division of these types, subsequently described, could naturally not be regarded.

Type I, given to most patients infected with Type I pneumococcus.* Type II antiserum was given to a few patients only.

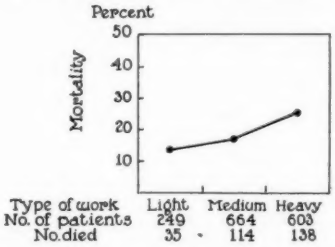


FIG. 1.—Lobar pneumonia. The curve of mortality according to occupation.

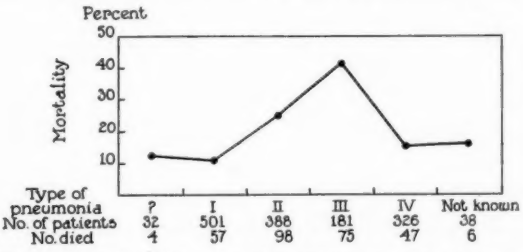


FIG. 2.—Lobar pneumonia. The curve of mortality according to the type of pneumococcus.

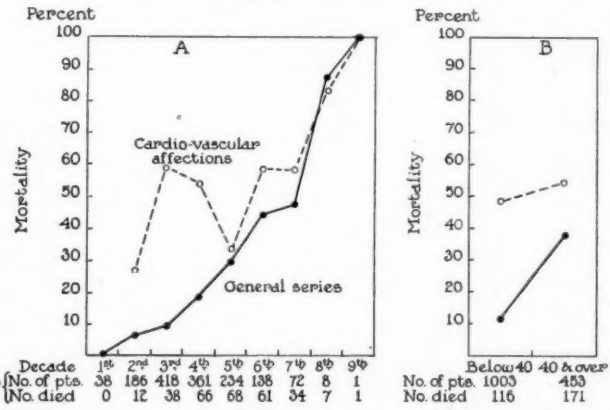


FIG. 3.—Lobar pneumonia. The curve of mortality: *A*, according to age; *B*, below and above age of 40.

But important as it is to recognize these individual risks and to assign relative values to them, it is more important still, as has

* The justification for omitting a further analysis of the influence of therapeutic serum in lobar pneumonia due to pneumococcus Type I, is that cases belonging to this group are regarded in this study as exhibiting a "benign" rather than a "disadvantageous" factor (Fig. 9), except under those circumstances indicated in the footnote to Table 4.

been pointed out, to understand that patients present them not in isolation but in combination. Patients are wholes.

When *none* of the untoward factors was present death was rare, there being only 2 deaths among 288 patients (0.69%) (Fig. 10).*

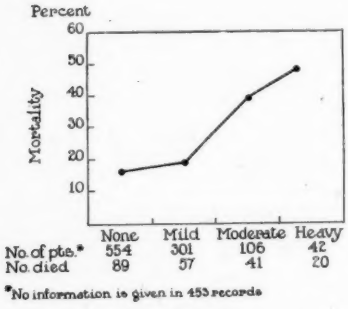


FIG. 4

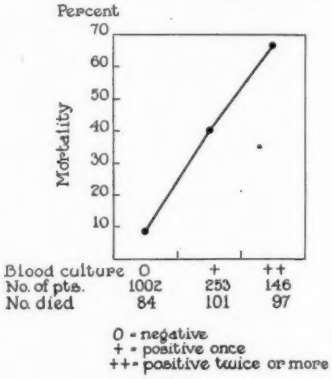


FIG. 5

FIG. 4.—Lobar pneumonia. The curve of mortality according to the use of alcohol.

FIG. 5.—Lobar pneumonia. The curve of mortality according to the presence of bacteriemia.

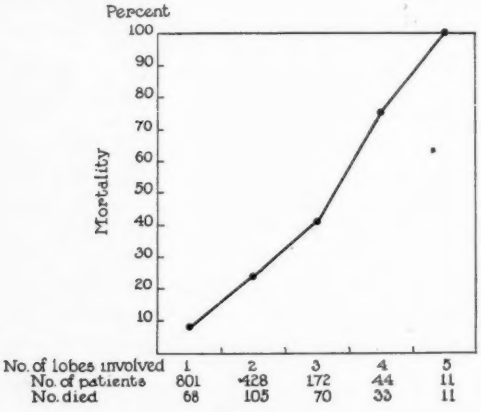


FIG. 6

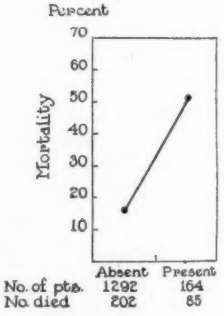


FIG. 7

FIG. 6.—Lobar pneumonia. The curve of mortality according to the number of pulmonary lobes involved.

FIG. 7.—Lobar pneumonia. The curve of mortality according to the presence of cardiovascular affections.

* The records of the 2 patients are:

1. A male clerk, aged 17, was admitted on the 11th day of his disease and died 14 hours later. Both lower lobes were involved. The sputum was rusty. The type of organism was not ascertained.

2. A young tailor, aged 21, was admitted on the 4th day of disease and died 25 hours later. The right lower lobe was involved with Type I pneumococcus. Blood culture was sterile. He was given 155 cc. antipneumococcus serum. His electrocardiogram was normal. At autopsy there was consolidation of the right lower lobe; there was absence (congenital ?) of the right middle lobe; the heart was negative.

TABLE 2.—LOBAR PNEUMONIA. MORTALITY WHEN ONE† AND TWO UNFAVORABLE FACTORS ARE PRESENT.

	A. Heavy work.			B. Pneumococ. Type II or III.			C. Age 40 and over.			D. Indulgence in alcohol.			E. Bacteriemia Type I or IV.			F. Three or more lobes involved.			G. Cardiovascular affections.			H. Unfavorable complications.		
	Total patients.	Died.		Total patients.	Died.		Total patients.	Died.		Total patients.	Died.		Total patients.	Died.		Total patients.	Died.		Total patients.	Died.		Total patients.	Died.	
		No.	%		No.	%		No.	%		No.	%		No.	%		No.	%		No.	%		No.	%
A. Heavy work	145	1	**0.69**																					
B. Pneumococcus Type II or III	64	4	6.2	124	3	**2.4**																		
C. Age 40 and over	29	0	0.0	59	8	13.6	67	3	**4.5**															
D. Indulgence in alcohol	16	1	6.3	7	0	0.0	10	2	20.0	12	1	**8.3**												
E. Bacteriemia	*34	3	8.8	25	9	36.0	*27	7	25.9	*4	2	50.0	*61	6	**9.8**									
F. Three or more lobes involved	9	1	11.1	19	2	10.5	8	2	25.0	1	0	0.0	*11	4	36.4	17	2	**11.8**						
G. Cardiovascular affections	7	0	0.0	8	2	25.0	11	2	18.2	..	..	...	*1	0	0.0	1	1	100.0	10	1	**10.0**			
H. Unfavorable complications	..	..	..	2	0	0.0	..	..	...	..	..	...	*2	1	50.0	..	..	..	..	..	...	1	1	**100.0**
Totals 355 Died 51 (14.4%)	159	9	..	120	21	...	56	13	...	5	2	...	14	5	...	1	1							

* This rubric relates to infection with Type I or Group IV (two unfavorable factors). Infection with Pneumococcus Type II or Type III results in three unfavorable factors.

† **Bold face type indicates the rate of mortality when single untoward factors were present.**

When *one* untoward factor only was present (Table 2; Fig. 11) the outlook was favorable or at least not unfavorable, though even under these circumstances the nature of the factor was not without

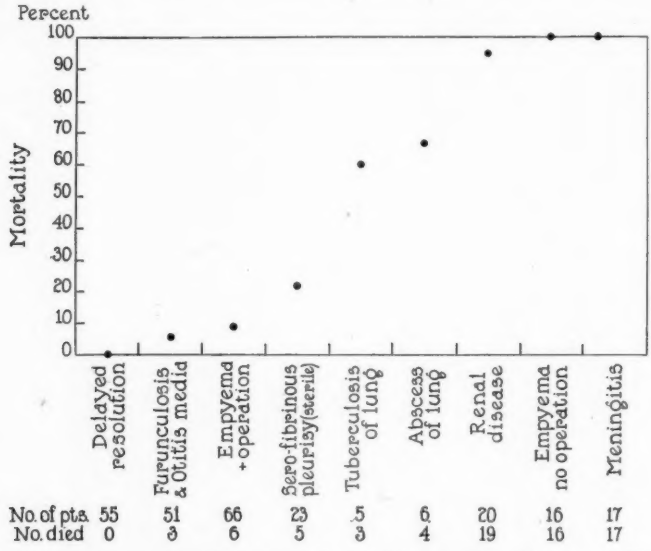


FIG. 8.—Lobar pneumonia. The curve of mortality according to the complications present, exclusive of cardiovascular affections.

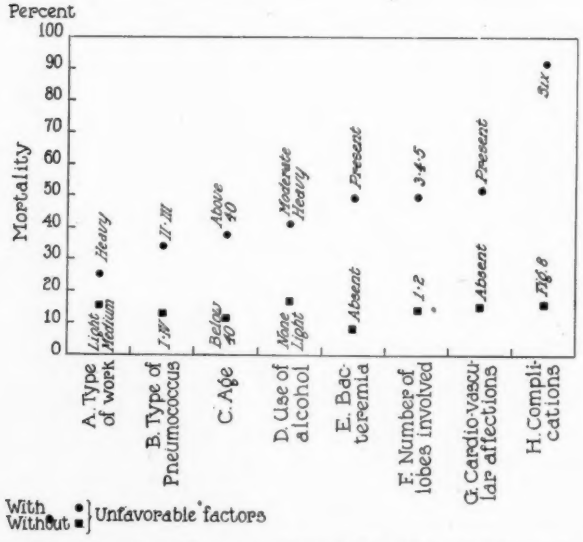


FIG. 9.—Lobar pneumonia. The curve of mortality with and without the presence of "unfavorable" factors.

importance. The number of patients who were observed in the Classes *F, G, H* was, however, too small to permit reliable inference. When *more than one* of the untoward factors was present the rate

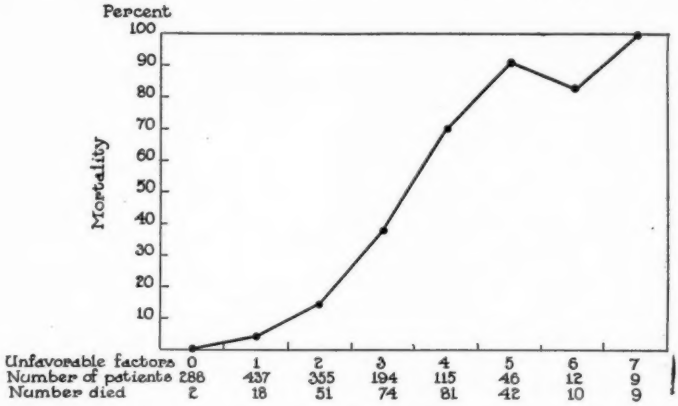


FIG. 10.—Lobar pneumonia. The curve of mortality according to the number of "unfavorable" factors.

of mortality rose (Fig. 10), depending on the number of them with which patients were obliged to deal. With *two* the rate was 14.4% (Table 2); with *three* it began to rise rapidly.

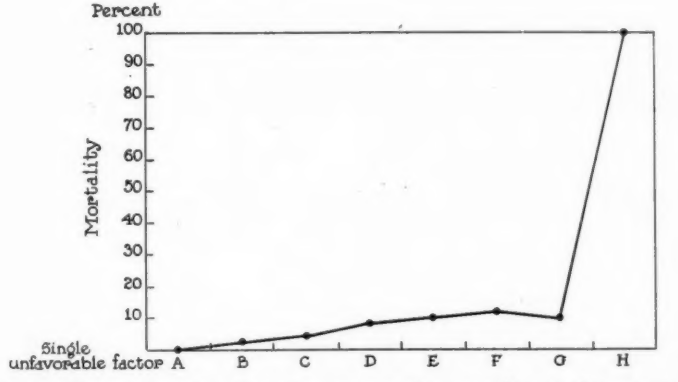
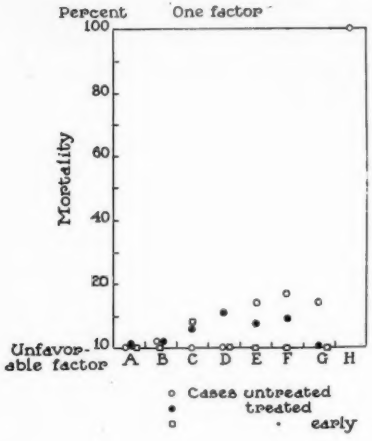


FIG. 11.—Lobar pneumonia. The curve of mortality according to the presence of single "unfavorable" factors. Category *H* includes only 1 case.

An attempt has been made to discover whether there is an arrangement or combination of factors which would prove to be more or less likely to influence the course of pneumonia than another combination. There was studied first what the result would be if any two factors were placed in combination, then any three, and so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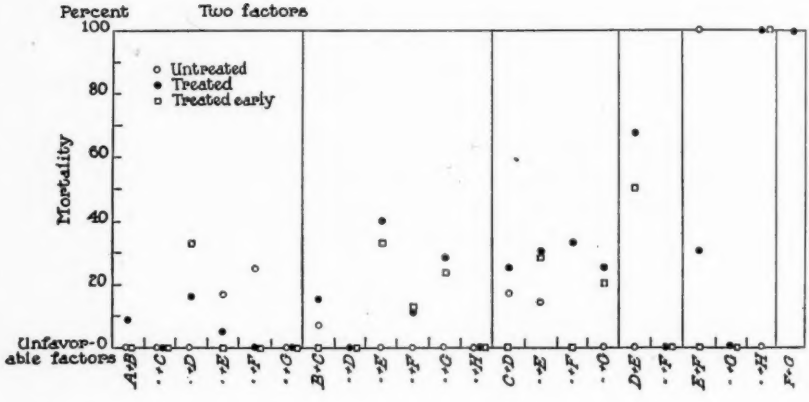
Percent
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Mortality
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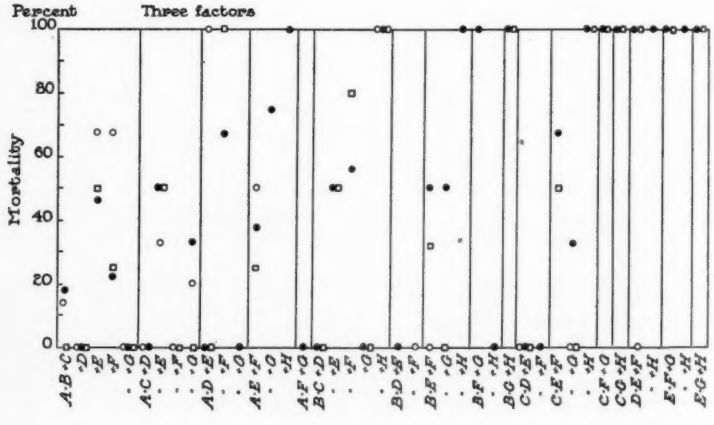
Percent
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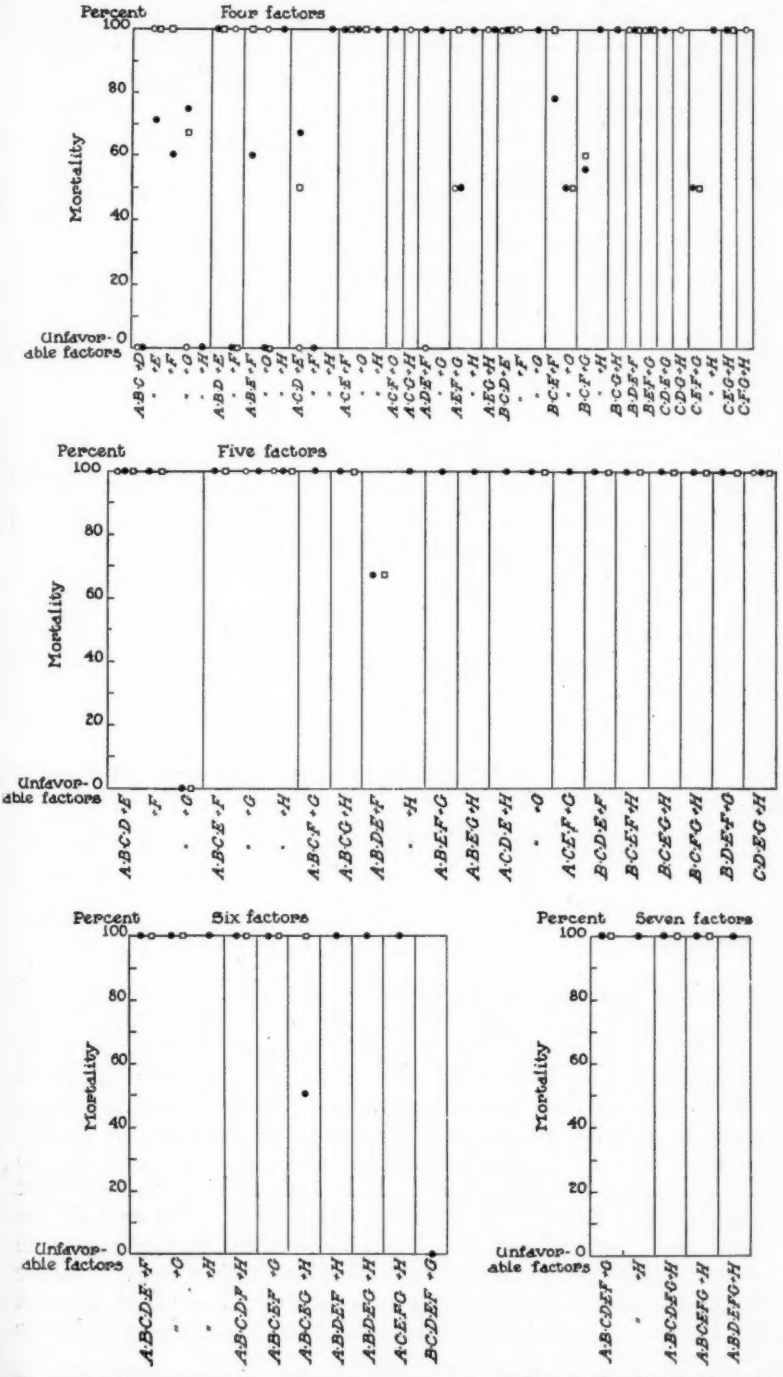

FIG. 12.—Lobar pneumonia. Mortality is shown according to the distribution of eight unfavorable factors in every actual combination.

TABLE 3.—LOBAR PNEUMONIA. MORTALITY OF PATIENTS TREATED WITH AND WITHOUT DIGITALIS.

ALL PATIENTS.			DIGITALIS. In First 72 Hours of Disease.																		
					No unfavorable factor.			One unfavorable factor.			Two unfavorable factors.			Three unfavorable factors.			Four unfavorable factors.			Five unfavorable factors.	
No.	Died.	Mortality, %	Group.	Dose, gm.	No. pts.	No. died.	Mortality, %.	No. pts.	No. died.	Mortality, %.	No. pts.	No. died.	Mortality, %.	No. pts.	No. died.	Mortality, %.	No. pts.	No. died.	Mortality, %.	No. pts.	No. died.	Mortality, %.
			I	0.1–0.6	30	0	0	31	1	3.23	18	1	5.55	6	1	16.7						
			II	0.7–0.8	13	0	0	14	0	0.0	13	1	7.7	7	2	28.6	3	..	..			
			III	0.9–1.5	28	0	0	70	1	1.43	70	7	10.0	35	14	40.0	20	8	40.0	3	2	66.7
			IV	1.6–+	3	0	0	20	1	5.0	21	3	14.3	14	6	42.9	8	6	75.0	2	2	100.0
698	117	16.7	Total		74	0	0	135	3	2.22	122	12	9.84	62	23	37.1	31	14	45.2	5	4	80.0
			After 72 Hours.																		
			V	0.1–0.6	28	1	3.6	43	1	2.3	26	8	30.8	22	16	72.7	7	5	71.4	1	1	100.0
			VI	0.7–0.8	5	0	0	27	1	3.7	17	5	29.4	5	3	60.0	5	3	60.0	1	1	100.0
			VII	0.9–1.5	30	0	0	70	4	5.7	77	13	16.9	40	13	32.5	18	7	38.9	3	2	66.7
			VIII	1.6–+	6	0	0	16	2	12.5	27	6	22.2	22	8	36.4	6	4	66.7	1	1	100.0
758	170	22.4	Total		69	1	1.45	156	8	5.1	147	32	21.8	89	40	44.9	36	19	52.8	6	5	83.3
Total 1,456	287	19.7																			
			Mortality of Patients Untreated and Treated With Digitalis.																		
			Digitalis		143	1	0.70	291	11	3.78	269	44	16.3	151	63	41.7	86	67	77.9	20	19	95.0
			No digitalis		145	1	0.69	146	7	4.79	86	7	8.1	43	11	25.6	20	14	70.0	5	4	80.0
			Difference				+0.01			−1.01			+8.2			+16.1			+7.9			+15.0
			Mortality of Patients Untreated and Treated With Digitalis Groups II and III.																		
			Digitalis Groups II and III		41	0	0	84	1	1.19	83	8	9.6	42	16	38.1	24	20	83.3	6	5	83.3
			No digitalis		145	1	0.69	146	7	4.79	86	7	8.1	43	11	25.6	20	14	70.0	5	4	80.0
			Difference				−0.69			−3.60			+1.5			+12.5			+13.3			+3.3

* See Fig. 15.

on to any eight factors (Fig. 12). But all these efforts have been without great significance. When *E*, *F*, *G*, *H* are elements in the combination the mortality is higher, but the numbers in these groups, occurring in isolated fashion, or indeed in any fashion at all, are too small for reliable calculation. Except for this reservation, the inference seems to be justified that the presence of what may be "extras" in the disease lobar pneumonia has a bearing on the outcome. The number of them with which a patient must grapple has obviously an important influence. It is desirable to know what added burden each one contributes, but to be certain what this is, the numbers available in this and in other studies are too small to ascertain. The untoward factors of which account has been taken are obviously heterogeneous. Some have and some

WITH DIGITALIS. GROUPED ACCORDING TO THE NUMBER OF UNFAVORABLE FACTORS.*

	Digitalis. In First 72 Hours of Disease.														Without Digitalis.		
	Four unfavorable factors.			Five unfavorable factors.			Six unfavorable factors.			Seven unfavorable factors.			No.	Died.	Mortality, %	No.	Died.	Mortality, %
	No.	No. died.	Mortality, %	No. pts.	No. died.	Mortality, %	No. pts.	No. died.	Mortality, %	No. pts.	No. died.	Mortality, %						
Three unfavorable factors.	3	75.0	6	6	100	1	1	100	1	1	100	97	14	14.4			
	..	..	1	1	100	0	..	..	0	..	..	48	4	8.3			
	20	83.3	7	7	100	3	3	100	1	1	100	238	53	22.3			
	8	80.0	6	4	66.7	1	1	100	1	1	100	76	24	31.6			
	31	79.5	20	18	90.0	5	5	100	3	3	100	459	95	20.7	239	22	9.2
After 72 Hours.																	
	7	63.6	1	1	100	1	1	100	3	3	100	135	38	28.2			
	5	71.4	1	1	100	1	1	100	0	..	..	63	16	25.4			
	18	75.0	9	8	88.9	4	2	50	2	2	100	256	60	23.4			
	6	40.0	7	7	100	1	1	100	1	1	100	95	31	32.7			
	36	63.1	18	17	94.4	7	5	71.4	6	6	100	549	145	26.5	209	25	12.0
												1,008	240		448	47	
Mortality of Patients Untreated and Treated With Digitalis.																	
	67	70.5	38	35	92.1	12	10	83.3	9	9	100						
	14	70.0	8	7	87.5	0	..	..	0	..	..						
		+0.5			+4.6												
Mortality of Patients Untreated and Treated With Digitalis Groups II and III.																	
	20	83.3	8	8	100.0												
	14	70.0	8	7	87.5												
		+13.3			+12.5												

have no necessary connection with lobar pneumonia. They have only this importance, that they are presented by patients during the course of this disease.

II.

Having separated the cases into groups according to their severity it became possible to study the effect of the action of digitalis in each group. Since the time in the course of the disease at which digitalis is given might exert an influence, this point has been taken into account. In those who recovered the duration ends with crisis or lysis in 7.9 days; in those who died, in 7.88 days. "Early" has been regarded, therefore, as the first 72 hours (Fig. 13); "late," as the remainder of the duration. Since digitalis was given, so far as concerns the entire experience, in an irregular manner, it

has been necessary to take dosage also into consideration. There are patients who took none; others who took small (Groups I and V), moderate (Groups II and VI), sufficient (Groups III and VII) and large amounts (Groups IV and VIII). Each group was divided

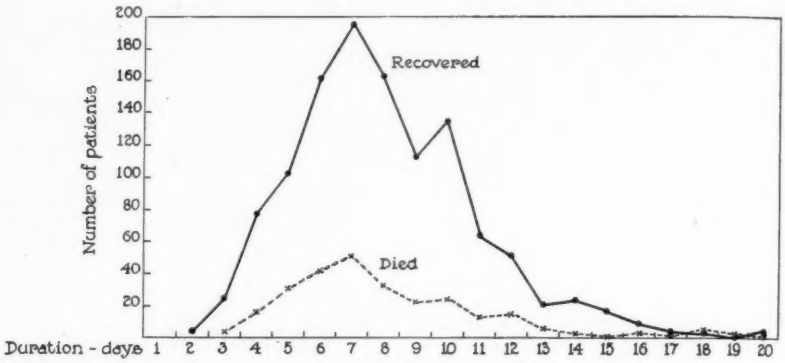

FIG. 13.—Lobar pneumonia. This curve shows the number of cases of recovery and of death according to the number of days of illness. The average duration of illness of the *recovered* cases, excluding 7 cases lasting longer than 20 days, was 7.9 days; of *fatal* cases, excluding 11 cases lasting longer than 20 days, was 7.88 days; of all cases was 7.89 days.

according to whether digitalis was taken early or late. Except for the patients to whom strophanthin was given, digipuratum or digitan (Knoll, Merck) has been used almost uniformly. Since 0.9 to 1 gm. has affected the ventricular rate of patients the subject

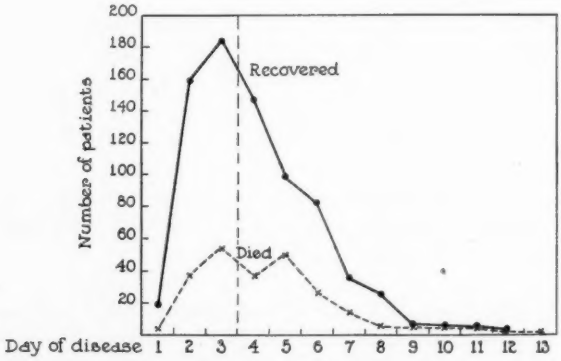

FIG. 14.—Lobar pneumonia. This curve shows the number of cases of recovery and of death according to the day on which digitalis was first administered. The first 3 days are regarded as being "early" in the course of the disease.

of auricular fibrillation ill of pneumonia, 0.9 to 1.5 gm. has been taken to be a "sufficient" dose. The cases have been divided, therefore, in groups, depending on the time of administration

(Fig. 14) and on size of the dose of digitalis administered (Table 3). These considerations have been utilized in analyzing the effect of giving digitalis to patients, depending on the "severity of disease," severity being expressed in terms of the number of untoward phenomena which developed in its course (Table 3). The tables show that there appears to be little difference whether digitalis was taken or not, except when two, three and five untoward factors were present (Table 3). If a sufficient dose (0.9 to 1.5 gm.) was given "early" (Fig. 15) the mortality was less than when no digitalis was taken in those without or with one untoward factor; it was greater otherwise, but the difference is not important. If the time when digitalis was given is regarded, the mortality was less in those with-

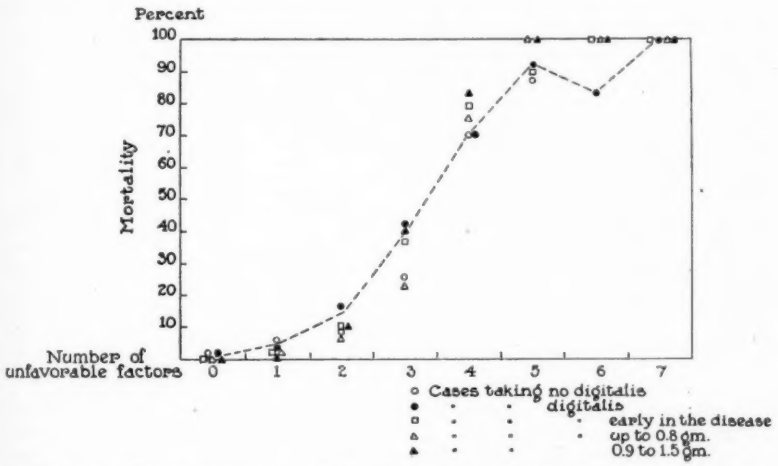

FIG. 15.—Lobar pneumonia. The mortality is exhibited of patients when untreated and treated with digitalis, when digitalis was given early, and when up to 0.8 gm., and when 0.9 to 1.5 gm. were given, early in the disease. The broken line describes the curve of mortality of the general series.

out or with one untoward factor; otherwise it was greater, but again the difference is slight. If small doses of digitalis (up to 0.8 gm.) were given the death rate was smaller when there were none, one, two or three of these factors. But the differences again are small.

The attempt finally has been made to discover whether, among the untoward elements, certain ones, when they were present alone, played a rôle more or less unfavorable than others when digitalis was given. The aged and the alcoholic were not aided; otherwise it did no harm (Table 4). Where the differences appear large in either direction the numbers of cases are too small to yield significant results. Whether digitalis was given or was not, whether the size of the dose was small or, in our judgment, adequate, whether it was given early or late—all of these considerations appear to be

of no deciding consequence. The form of the curve of mortality (Fig. 15) depends, it seems, entirely on the degree of severity of the affection; when it is slight, death is rare; the more severe, the greater the number of untoward factors against which the struggle must be made, the smaller become the chances of recovery. The form of the curve appears to indicate what the important factor is in deciding the outcome; it is the disease—virulence of the infection and resistance of the host, both together, rather than the action of digitalis.

TABLE 4.—LOBAR PNEUMONIA. MORTALITY OF PATIENTS TREATED AND UNTREATED WITH DIGITALIS EXHIBITING A SINGLE UNFAVORABLE FACTOR.

	No digitalis.			Digitalis.			Difference in mortality, %.
	No. of patients.	Died.	Mortality, %.	No. of patients.	Died.	Mortality, %.	
A. Heavy work	48	0	0.0	97	1	1.03	1.03
B. Type II or III* pneumococcus	43	1	2.33	81	2	2.47	0.14
C. Over 40 years of age	17	0	0.0	50	3	6.00	6.00
D. Moderate or heavy use of alcohol	3	0	0.0	9	1	11.1	11.1
E. Bacteriemia* Type I or Group IV	21	3	14.3	40	3	7.5	−6.8
F. Three or more* lobes involved	6	1	16.7	11	1	9.1	−7.6
G. Cardiovascular affection	7	1	14.3	3	0	0.0	−14.3
H. Unfavorable complications	1	1	100.0				
Total	146	7	4.79	291	11	3.78	−1.01

* The presence of infection with Pneumococcus Type I or Group IV is not counted as an untoward factor except when it invades the blood stream or when 3 or more lobes are involved. Pneumococcus Type II and Type III when they are accountable for the existence of lobar pneumonia and are present also in the blood or when 3 or more lobes are involved are counted as two factors; cases so affected are not included in this table.

III.

If, in this stage of the analysis an interpretation were adopted which would be regarded as reasonable, it would be that giving digitalis to patients with lobar pneumonia does not influence the rate of mortality; this method of analytical treatment points neither to an unfavorable nor to a beneficial action. But numerous physicians[6–15] maintain the belief that the course of disease in those to whom digitalis has been given is influenced nevertheless. The difficulty consists, has indeed consisted, in putting this belief to test. If the method of study so far adopted leads to an *impasse*, another approach to solving this problem may be attempted.

The beneficial action of digitalis is most convincing in patients with certain affections of the heart, of course not subjects of lobar pneumonia. Proof that digitalis acts upon the heart is no longer

necessary. That it acts also upon the febrile heart in pneumonia[1] seems now generally to be accepted. Aside from having an influence on the size of the heart in pneumonia, digitalis exercises its well-known action on conduction by reducing the rate of the ventricles in auricular fibrillation. The view has been expressed that it is precisely in cases of auricular fibrillation[2,10–13] and auricular flutter in which, because with the onset of these irregularities serious symptoms develop, perhaps resembling the state sometimes called collapse, giving digitalis actually has a beneficial action. As a result of early experiences in the Hospital of the Rockefeller Institute the point was made that, since many cases of auricular fibrillation and flutter occurred (11 in 123, 9.7%) in which it did good,

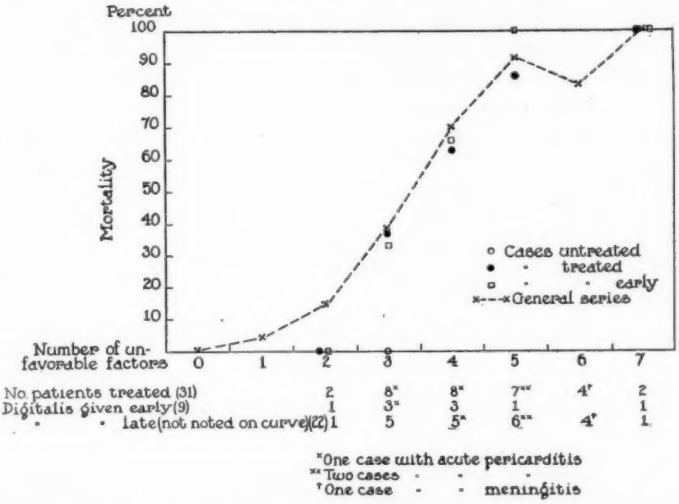

FIG. 16.—Lobar pneumonia and auricular fibrillation. The mortality of patients untreated and treated with digitalis according to the number of "unfavorable" factors, of which auricular fibrillation or flutter was one, which were present, exhibited in relation to the curve of mortality of the general series.

digitalis might be given as routine treatment with the view, in anticipation of its occurrence, of preventing harm due to this arrhythmia.[17] The point had not yet been appreciated that younger individuals rarely exhibited this irregularity; and that it occurred for the most part only beginning with the fifth decade. Since an effect occurred on heart muscle, as seen in changes in the *T* wave,[1] on the size of the heart[16] and on contraction with moderate doses, the statement[1] was made that action by digitalis could be counted on—whether for good was another matter. At all events, the effect on conduction in auricular fibrillation might prove to be life saving.

In the light of these reflections, the course of events in all the cases of auricular fibrillation and auricular flutter has been reviewed

(31 patients, of whom 18 [58%] died).* The cases have been analyzed, though the number is small, from the point of view of the general mortality, of the age of the patients, of the other untoward factors which they presented. It is apparent that, if the cases are grouped according to the number of the "untoward" factors against which they were required to contend, the outcome in those who suffered from two (of which auricular fibrillation was one) was strikingly better than that in the general series (Fig. 16). When there were three factors (of which auricular fibrillation was one) the death rate was actually lower than the rate in the case of those who took digitalis (Fig. 16). The 3 patients who died were seriously ill (Fig. 16). When there were more untoward factors there was no important difference from the general curve of mortality. The influence of age on the development of auricular fibrillation is not certain; the number of cases is too small. One only occurred before the age of 30; the incidence then rose to the age of 60 and in the seventh and eighth decades fell (Fig. 17).†

Whatever may be learned from greater experience concerning the influence of fibrillating auricles on the outcome of lobar pneumonia, this at all events is apparent from the few observations which it has been possible to make; the chances in those in whom it is present are not worse than in other patients (Fig. 16). Giving digitalis has been useful when no more than two untoward elements (besides auricular fibrillation itself) were present; the rate of mortality was favorably influenced. When there were more untoward

* A table containing full data of these cases has been made and will gladly be placed at the disposal of those who are interested in studying it.

† Several notes concerning the cases in which auricular fibrillation occurred deserve record:

Of 31 patients taking digitalis:

1. (*a*)	Auricular fibrillation persisted until death	8 (26%)	8
	Auricular fibrillation persisted in recovery	1 (3%)	
(*b*)	Ventricular rate slowed	23 (74%)	
(*c*)	Normal rhythm returned	22 (71%)	
	Of whom 12 (39%) recovered		
	Of whom 10 (32%) died		10
			18

13 patients recovered:

2. (*a*)	Auricular fibrillation developed before taking digitalis	8
(*b*)	Auricular fibrillation developed after taking digitalis, 1 gm. . . .	2
(*c*)	Auricular fibrillation developed after taking digitalis, less than 0.9 gm.	3
		13

18 patients died:

3. (*a*)	Auricular fibrillation developed before taking digitalis	6
(*b*)	Auricular fibrillation developed after taking digitalis, 0.5 gm. . .	1
(*c*)	Auricular fibrillation developed after taking digitalis, 1 to 2.2 gm. in 2 to 5 days	11
		18

Number of cases before taking digitalis	(*a*) 14 (2*a* + 3*a*)	of whom 6 died (42.9%)
Number of cases having taken a sufficiency of digitalis	(*b*) 13 (2*b* + 3*c*)	of whom 11 died (85.0%)

elements, the chances were not worse than they would otherwise have been.

Although there is no reason to believe that the study of patients suffering from other forms of cardiac affection can throw light on

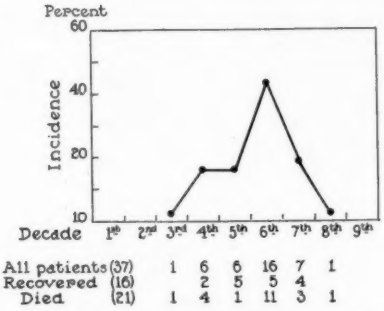

FIG. 17.—Lobar pneumonia and auricular fibrillation. This curve exhibits the patients arranged according to age.

the value of giving digitalis, the experience gained from 164 cases in which some form of cardiac affection was detected has been analyzed. Mortality according to age lay higher in the earlier decades in relation to the general series than in the later ones

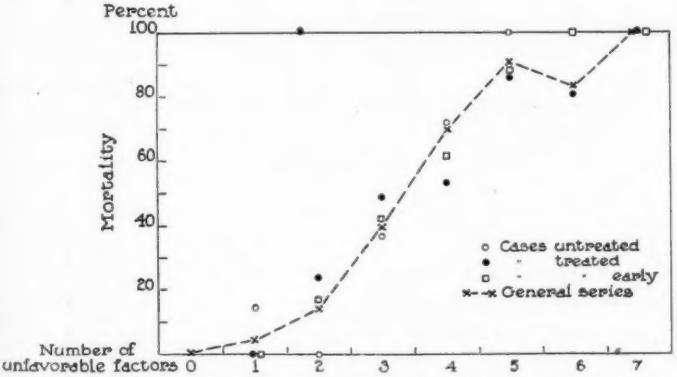

FIG. 18.—Lobar pneumonia and cardiovascular affections. The mortality of patients untreated and treated with digitalis, according to the number of "unfavorable" factors, of which cardiovascular affections was one, which were present, exhibited in relation to the curve of mortality of the general series. Compare Table 7.

(Fig. 3). A variety of irregularities and of organic diseases (of the valves, arteriosclerosis and hypertension, acute pericarditis) were encountered (Tables 5 and 6). In these cases the influence of the action of digitalis on the curve of mortality exhibits no important

difference from that which occurred in the general series (Table 7; Fig 18).

TABLE 5.—LOBAR PNEUMONIA AND CARDIOVASCULAR AFFECTIONS. MORTALITY ACCORDING TO TYPE OF AFFECTION.

Type of affection.	Number.	Died.	Mortality, %.
A.*			
Arrhythmia:			
Premature contractions	49	20	41.7
Auricular fibrillation	37	21	56.8
Valvular disease	27	14	51.9
Coronary sclerosis Hypertension Arteriosclerosis	28	16	57.5
Acute pericarditis	29	29	100.0
B.†			
Heart block	23	3	13.1

* See Figs. 3 and 7.
† See Table 6.

TABLE 6.—LOBAR PNEUMONIA AND HEART BLOCK.

Case No.	Age, years.	Type of heart block.	Auriculo-ventricular conduction time, sec.	Occurrence of heart block; relation to fever.	Amount given before onset of heart block.	Duration of heart block.	Result.
1072	40	2:1 Auricular fibrillation	Increased Varying	During	Strophanthin 3 x 1 mg. i.v.	Transient	Recovered
4046	69	Long *A–V* interval and 2:1 Auricular fibrillation	0.12–0.38	During	Strophanthin 2 x 1 mg. i.v. Digitalis 2.5 gm.	Transient	Died
3488	24	Long *A–V* interval and 2:1	0.18–0.34	During	Digitalis 2.6 gm.	Transient	Recovered
5698	34	Long *A–V* interval and 2:1	0.22–0.34	During	Digitalis 1.1 gm.	Transient	Recovered
6164	31	Long *A–V* interval and 3:2	Increased Varying	During	Digitalis 2.0 gm.	Transient	Recovered
5206	28	3:2	0.20	During	Digitalis 0.8 gm.	Transient	Recovered
2247	43	Long *A–V* interval and 2:1	0.22–0.34	During	Digitalis 2.9 gm.	Transient	Died
7904	65	Left bundle branch block (0.14 seconds)	0.16	During	Digitalis 0.9 gm.	Permanent	Died
3164	22	Long *A–V* interval and 2:1	Increased Varying	During and after	Digitalis 1.5 gm.	Transient	Recovered
6922	15	2:1	Increased Varying	After	Digitalis 1.1 gm.	Transient	Recovered
2102	18	Occasional blocked auricular beats	0.22–0.28	After	Digitalis 1.9 gm.	Transient	Recovered
3658	19	Long *A–V* interval and 2:1	0.12–0.28	After	Digitalis 2.0 gm.	Transient	Recovered
2381	23	Long *A–V* interval and 2:1	0.18–0.32	After	Digitalis 2.1 gm.	Transient	Recovered
2222	26	Long *A–V* interval and 2:1	0.15–0 34	After	Digitalis 1.5 gm.	Transient	Recovered
5427	32	2:1 and 3:1	Increased Varying	After	Digitalis 1.1 gm.	Transient	Recovered
3169	45	2:1	Increased Varying	After	Digitalis 3.1 gm.	Transient	Recovered
3914	56	2:1	Increased Varying	After	Digitalis 2.0 gm.	Transient	Recovered
6664	34	Sino-auricular block	Increased Varying	After	Digitalis 1.0 gm.	Transient	Recovered
5077	42	Occasional blocked auricular beats	Increased Varying 0.24–0.26	After	Digitalis 0.9 gm.	Transient	Recovered
3319	18	3:2	Increased Varying	After	Digitalis 1.6 gm.	Transient	Recovered
7308	56	Slight right intraventricular block (0.12 second)	0.14–0.16	After	Digitalis 1.0 gm.	Transient	Recovered
6574	42	Slight right intraventricular block (0.12 second)	0.16	During and after	Digitalis 1.0 gm.	? Permanent	Recovered
4131	34	Right intraventricular block (0.16 second)	0.13	During and after	.....	Permanent	Recovered

TABLE 7.—LOBAR PNEUMONIA AND CARDIOVASCULAR AFFECTIONS. MORTALITY OF PATIENTS UNTREATED AND TREATED WITH DIGITALIS ACCORDING TO NUMBER OF UNFAVORABLE FACTORS OF WHICH A CARDIOVASCULAR AFFECTION WAS ONE.*

No. of unfavorable factors.	No digitalis.			Digitalis.								
				All patients.			Digitalis given early.			Digitalis given late.		
	No. of patients.	Mortality.		No. of patients.	Mortality.		No. of patients.	Mortality.		No. of patients.	Mortality.	
		No.	%.		No.	%.		No.	%.		No.	%.
1	7	1	14.3	3	0	0.0	1	0	0.0	2	0	0.0
2	6	0	0.0	22	5	23.6	12	2	16.7	10	3	30.0
3	11	4	36.4	33	16	48.5	12	5	41.7	21	11	52.4
4	7	5	71.4	34	18	52.9	18	11	61.0	16	7	43.8
5	2	2	100.0	21	18	85.7	8	7	87.5	13	11	84.6
6	..	..	....	10	8	80.0	3	3	100.0	7	5	71.4
7	..	..	....	8	8	100.0	3	3	100.0	5	5	100.0
Total	33	12	36.4	131	73	55.7	57	31	54.4	74	42	56.8

* See Table 5 A.

Discussion. Mention recurs unfortunately with too great frequency of the value of digitalis in the cure of lobar pneumonia. The thought that digitalis can have a bearing on the outcome of the disease itself should disappear. When this idea was originally suggested,[18] relatively little was known either concerning the nature of pneumonia or the action of this drug. It was the fall in temperature which attended the use of large doses that suggested to Traube and others its availability as an antipyretic. No one believes now that digitalis has this property. Another belief concerning its action is bound up with the word beneficial. Beneficial can be used in two senses: (1) Connected with an effect on the disease itself and (2) with the effect on some occurrence, precipitated during its course.

(1) To be beneficial as concerns the disease itself requires proof that there is a relation between the action of digitalis and the pulmonary process. Since there is no evidence for this supposition, this notion also can be dismissed. But (2) that taking digitalis has an effect on a physiologic process (auricular fibrillation) apart from but precipitated in the course of the disease is, however, fairly established.[1,2,3] Conclusions formerly published[1] state that: "(1) Digitalis acts during the febrile period in pneumonia. (2) It produces a beneficial, possibly a life-saving effect in cases of auricular irregularity (fibrillation and flutter). (3) Whatever beneficial action it has on the function of the normally beating non-febrile heart may be expected from its use in the febrile heart of pneumonia." These conclusions point obviously to the action of digitalis on the

heart and not to an action on the immunologic processes of the disease, lobar pneumonia. For these reasons it seems gratuitous to speak of a beneficial effect of the action of digitalis on the rate of mortality. Unless current conceptions dealing with the nature of pneumonia were incorrect, this notion should no longer be suggested. It is only when some untoward accident, like fibrillation of the auricles, occurs that giving digitalis may be regarded as an aid; if people were otherwise to die of this accident, digitalis may be regarded as life saving—but only in this sense and only in this connection. When it was first discovered that transient auricular fibrillation occurred in lobar pneumonia and that it seemed furthermore to occur frequently (9.7% of cases), "as a result of these experiences, the hospital (of the Rockefeller Institute) *for the time being** adopted the following rules in the treatment of pneumonia. . . ."[19] With more experience and for reasons already detailed, practice in this regard has changed.

If the use of an agent is found to be beneficial in one respect, as in the management of transient auricular fibrillation, care must be exercised nevertheless to see to it that it is not harmful in another, as in the outcome of lobar pneumonia itself. The evidence, not yet conclusive, indicates that the action of digitalis is without influence on the rate of mortality under a variety of circumstances.

This inference differs from that of Niles and Wyckoff and Wyckoff, DuBois and Woodruff. It is perhaps striking that the difference between their treated and untreated cases is as little as 7.7% (Table 5).[2] This is within the error of most physical, to say nothing of biologic, measurements and speaks for the correctness of the inference in the present study. Why the results of these two studies varies is not certain. The nature of the cases may not have been fundamentally different. Perhaps the difference in technique of the analyses employed in the two hospitals is responsible for the difficulty. And yet when the crude figures alone are regarded, the rate of mortality in both favors the untreated cases. It did in fact occur, as in the experience of other observers, that the patients more severely ill in our hospital took digitalis rather than the others. A conclusion should not depend, however, on so simple a comparison. In the attempt to make comparison valid, reliance has been placed on treating a large number of cases, though perhaps not large enough; since sufficiently large numbers are scarcely available, it has been necessary to resort to some sort of weighing of the evidence.

Essentially it is weighing which has been attempted in this study. Other methods have been employed. Bullowa[5] used the method of rating the severity of each of five main factors, the value given to each factor being, of course, arbitrary. But the reason for doing so is clear: The method of alternation to secure

* Italics not in original.

controls cannot, in a relatively small group of cases, be undertaken otherwise with justice. The factors which Bullowa rated depend, with the exception of age, pregnancy, and obesity, on phases of the disease. With a different choice of the exceptions, the method this study has pursued is similar. It is possible that, again with a few exceptions, such as *E, F, G, H*, the factors chosen for analysis are of small importance as long as certain ones like bacteriemia are included. The total load patients must bear decides the outcome. Adding other factors like pregnancy, obesity, psychologic disturbances, gastro-intestinal distress, cyanosis, naturally increases the number of variables to 13 and necessitates the accumulation of *still* greater numbers of cases, if justifiable inferences as between the effect on treated and untreated cases are to be drawn.

The matter of weighting becomes the more important when the difficulties are reviewed which unavoidably enter a research so complicated as this. Wyckoff, DuBois and Woodruff, and Niles and Woodruff encountered difficulty with their digitalis Specimen B, which they gave to 142 (42%) of their patients. Now the assay of B was twice that of the other specimens used and the rate of mortality was 10% higher. But when Specimen B made patients ill, the rate of mortality was only 24.6% as against 64.2% when it was not toxic, and as against a rate of 33.7% for the untreated cases. In short, the stronger, toxic, digitalis reduced the rate by 9.1% below that of the untreated cases. In another connection it appears that, when bacteriemia was an unfavorable factor, those who were treated with digitalis were better off by 0.4% than the untreated cases; but freedom from bacteriemia, in those likewise treated with digitalis, reduced their chances of recovery by 14.3% as against those untreated. These are perhaps vagaries; but they are not of a nature to satisfy one of the competence of a method to yield insight into so complicated a situation.

Objections have been made to the use of digitalis in lobar pneumonia[20] on the ground: (1) That auricular fibrillation is rarely found except in dying hearts; and (2) that it has a tendency to excite the onset of auricular fibrillation. If the occurrence of auricular fibrillation is regarded from the viewpoint of the total experience, its incidence was small, 37 in 1456 (2.5%). But after the age of 40 there were actually 6.6%, and under 40, only 0.7%. So far as the tendency to excite the onset of auricular fibrillation is concerned, the evidence to which Wolferth[20] referred is meager. Robinson,[21] in describing his patient, says: "The administration of digitalis may have been a factor in causing the disappearance of auricular fibrillation on two occasions." But neither his case nor others reported in the literature*[,23,24] occurred in lobar pneumonia. In this series 14 cases occurred before taking digitalis (Foot-

* Resnik deals critically with the cases collected by Robinson.[22]

note, p. 474, $2a + 3a$). A relation may exist, but the evidence so far is scarcely conclusive. It is noteworthy that in 1008 patients, auricular fibrillation was detected no oftener than 35 times (3.5%) among those who took digitalis (including those who took strophanthin). It is worth noticing also that of 31 patients who took digitalis (not strophanthin), the normal rhythm returned in 22, and that 10 of these died. Of the 18 who died, auricular fibrillation persisted until death only in 8 (Footnote 1. (*a*) p. 474). In attempting to understand this occurrence, the suggestion may be made either that the mechanism of the approach of death had nothing to do with the onset or persistence of this arrhythmia or that there is present in the mechanism of death a factor which inhibits a continuance of the irregularity. But in the latter case it would then be difficult to understand why auricular fibrillation was present until death in 8 cases. So far as its being rare except in the dying heart is concerned, it was possible to say "The fact that so many died without changes must be taken to mean that the proximity of death was not associated with the electrocardiographic changes on which we rely, even in those who had taken small amounts of the drug."[1]

Further observations have been made on changes in heart block during lobar pneumonia. The statement was formerly made[1] that, when digitalis was not given, although alterations in conduction occurred in both directions, the degree was not significant. A decrease, not greater than 0.06 second was observed in 11 patients and an increase, not greater than 0.03 second, in 4 patients. When digitalis was given, there was almost uniformly (80%) an increase of 0.04 second or more, leading in 7 instances to block. The patients were all in the febrile stage. Altogether 23 cases of heart block have been observed (Table 6), lesser grades of change in conduction have not been studied. It appears that 8 cases occurred during fever, but that in each case sufficient digitalis (or strophanthin) was given to bring about the arrhythmia. Reports of heart block in cases of lobar pneumonia have appeared in which this irregularity occurred during the febrile stage both with[25,26,27] and without[28,29*] the administration of digitalis; cases have also been reported as occurring during the afebrile period of convalescence, again with[29] and without[30†,31,32] taking digitalis. The distinction between the febrile and postfebrile periods is sometimes not made[33] on the supposition that it is not important. Mention whether digitalis was given is sometimes omitted.[34] It is desirable to know the mechanism in those cases to which digitalis has not been given and in which block occurs after the subsidence of fever. Heart block appearing then apparently does not necessarily depend on taking digitalis.

* There is no specific statement on whether digitalis was given.
† This was a case of influenza pneumonia.

Summary. An analysis of 1456 cases of lobar pneumonia has been made, to ascertain what influence the action of digitalis has on the course of this disease. Since the method of comparing treated and untreated cases by alternating them could not be applied, that of weighing the cases was employed instead. The reasons why, in a situation in which there are many unavoidably varied factors, this method is preferable to the other, have been given. In weighing the cases, factors which are untoward or unfavorable were first isolated and then by regarding the presence of each of them as having a value of one, the cases were grouped according to the number of their untoward factors. The importance of the untoward factors in determining the rate of mortality has been emphasized. It appears from the curve of mortality drawn according to the number of these factors that the rate depends on the number present. When the groups are studied in the light of whether digitalis was taken and also according to the size of the dose and the time in the course of the disease when it was administered, it appears that not giving digitalis, but the "severity of the disease" was the factor which decided the outcome. The action of digitalis is, in short, regarded as having no necessary influence on the processes of lobar pneumonia *per se*. When the inference that giving digitalis is harmful,[2,3] except perhaps in cases of auricular fibrillation, is compared with the one drawn in this study, it is suggested that the difference may be due to the difference in the methods of analysis employed. Attention is drawn to the fact that, in an unweighted analysis, so slight a difference, in a relatively small series, between treated and untreated patients as 7.7%, should have been found.[2,3] Finally, the effort has been made to ascertain whether digitalis is useful in auricular fibrillation or auricular flutter in which the action of digitalis may be expected to be beneficial; it appears that in those cases in which the outcome depends on safeguarding patients from the unfavorable effects of the rapid rate in auricular fibrillation and auricular flutter the administration of digitalis may be life saving.

Digitalis should not be regarded as an agent necessarily having an influence on the natural history of the pneumonic or pneumococcic infection.

Conclusions. 1. Giving digitalis does not seem to influence the course of events in lobar pneumonia.

2. Its action, in favorable cases, in which auricular fibrillation and auricular flutter occur, appears to be beneficial.

3. The outcome in lobar pneumonia depends on the "severity of the disease," which in turn depends especially on the presence of bacteriemia, the number of pulmonary lobes involved, and the existence of complications.

4. It is not certain whether the action of digitalis precipitates

the occurrence of auricular fibrillation. If it does so, the number of cases is small, especially in the earlier decades.

5. The proximity of death does not determine the onset of auricular fibrillation. Even when it was present, it ceased in 10 of 18 cases before exitus.

6. Heart block did not occur during the febrile period of lobar pneumonia except in those cases to which a sufficient amount of digitalis was given to bring it about.

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PNEUMONIA IN UNDULANT FEVER.

A Report of Three Cases.

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Undulant fever, like other generalized infections, may manifest itself as a localized diseased process in one or more of the various parts of the body. The occurrence of arthritis, endocarditis, bronchitis, nephritis, orchitis, peritonitis, meningitis and other localizations during undulant fever have been reported as recent contributions to the knowledge of brucelliasis although they have been described many years before chiefly by the British Army Surgeons in Malta. Pneumonia occurring during the disease has been only briefly referred to since the recognition of brucelliasis in the United States.

Fionentini[2] isolated brucella from the sputum of a case of Malta fever with pneumonia, and brucella were also isolated from the pus of a case of empyema. Eyre[1] in discussing 1000 cases of Malta fever due to the caprine variety of brucella noted the occasional occurrence of pneumonia and suggested that the pulmonary lesions were specific in nature. Vanni[3] described pneumonia produced in the guinea-pig by the inoculation of brucella and stated that grossly the lesions could not be distinguished from pulmonary tuberculosis at necropsy and described cases of undulant fever in men with bilateral apical infiltration similar to those of tuberculosis. All of these studies concerned the caprine variety of brucella.

Reports of pulmonary lesions occurring in patients infected with the bovine or porcine strains are rare and incomplete. Hardy[7] reported bronchitis in one-third of his cases and suggested that it was probably due to brucella. Pulmonary abscess occurred in one of his fatal cases. He also observed pulmonary lesions of a bronchopneumonic character in a high percentage of inoculated guinea-pigs and suggested that similar lesions may occur in man. Curschmann,[4] Kristensen and Holm,[5] Attinger[6] and others report cases of undulant fever in senile patients terminating with bronchopneumonia probably due to other organisms which are common invaders in debilitating diseases of the aged. Bjurström[8] reported a case of brucelliasis with bilateral bronchopneumonia and a pleural effusion from which brucella were isolated. The course of the disease and the character of the pulmonary lesions in Bjurström's case is very similar to the cases reported in this article. Puech and Vidal[9] isolated a brucella-like organism from the pleural fluid obtained from a case of undulant fever.

Because of the clinical similarities and frequent diagnostic difficulties arising between undulant fever, pulmonary tuberculosis and other lung diseases, it is especially important to recognize that pulmonary involvement occurs in certain cases of the former disease. The cases in this report were originally considered as cases of pneumonia rather than undulant fever because of the predominance of pulmonary signs and symptoms.

Case Reports. Case 1.—R. T., a laborer, aged 55, began to notice marked fatigue about February 1, 1931, followed soon by chills, feverishness and drenching sweats. There were also severe joint pains, muscle soreness, backache and severe headache. The symptoms prevented the patient from working and at intervals necessitated bedrest for 2 or 3 days at a time. On April 12, he experienced severe lancinating pain in the lower left side of the chest aggravated by deep breathing and coughing. The cough soon became productive and as much as 8 ounces of serous mucoid sputum was raised daily. The development of pulmonary symptoms caused him to be sent to the hospital as a case of pneumonia on April 23.

On examination the patient was flushed, coughed frequently but appeared to be quite comfortable. There was slight cyanosis of the oral mucosa and finger nails. The expansion of the left lower side of the chest was diminished and posteriorly over this area there was a moderate impairment of resonance, increased tactile and vocal fremitus, high pitched breath sounds and an occasional coarse râle. The spleen was palpable.

Laboratory Data: Hemoglobin 78% (Sahli); 4,500,000 erythrocytes; 6000 leukocytes per c.mm., 70% of which were granulocytes and 28% lymphocytes. Several urine analyses were normal. The blood Wassermann reaction was negative. Agglutination tests on the serum showed complete agglutination of the brucella abortus antigen in a dilution of 1 to 160. Repeated examinations of the sputum for B. tuberculosis were negative.

Roentgen ray plates of the chest showed a diffuse increase of the bronchovascular markings and a triangular shaped area of diffuse haziness in the parenchyma of the left lower lobe near the periphery suggesting a chronic pulmonary fibrosis or a slowly resolving pneumonia. The temperature curve showed a daily afternoon elevation to around 38.9° C. (102° F.) associated with drenching sweats and chills or chilly sensations. The fever and the symptoms gradually subsided after 1 month of bedrest. The patient was discharged on May 30, afebrile, but with the signs of a slowly resolving parenchymal pneumonic lesion 7 weeks after its onset. Examination 6 weeks later, 13 weeks after the onset, showed that the lesion had entirely disappeared.

Case 2.—J. J., a farmer, aged 41. Prior to the spring of 1932, 3 cows in his herd aborted. The patient drank as much as 1 gallon of raw milk from his herd daily. He became ill in August, 1933 and first noted malaise and disinclination for his usual work. After short rest period he felt fit again. During September, 1933 the patient became more fatigued and began to experience severe aches and lameness throughout the various muscles and joints. About September 24, while working in the field, he developed a chill which lasted several minutes. He went to bed, began to feel hot, and perspired so profusely that his bedding became wet. There was severe occipital headache. After 1 day he left his bed to oversee the farmwork but that evening again developed chills, fever and sweating. The aching of the joints became more severe. About October 8, following one of the chills, he developed a severe sharp pain in the right side of the chest aggravated by inspiration. He then developed a cough and raised a

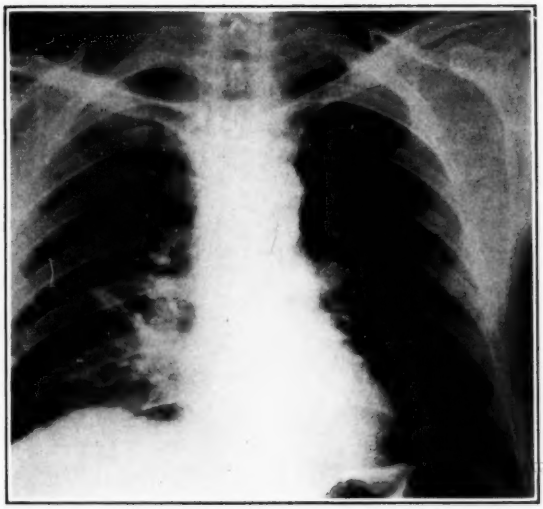

FIG. 1.—Case 2, taken 23 days after onset of pulmonary symptoms when lesion was most extensive, showing an area of diffuse density in the medial inferior portion of the right lung.

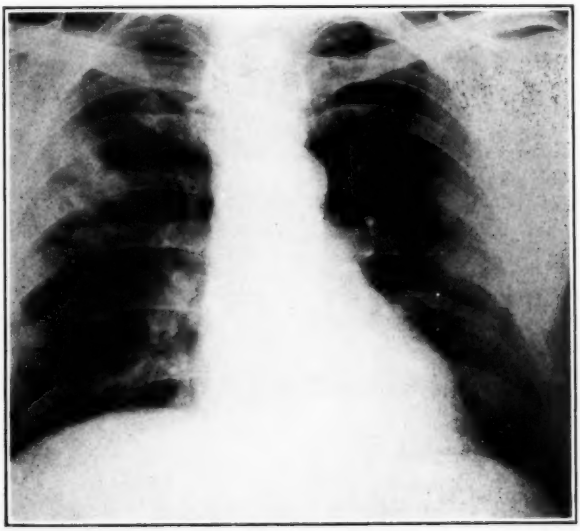

FIG. 2.—Case 3, taken 14 days after onset of pulmonary symptoms showing maximum involvement of lower portion of right upper lobe.

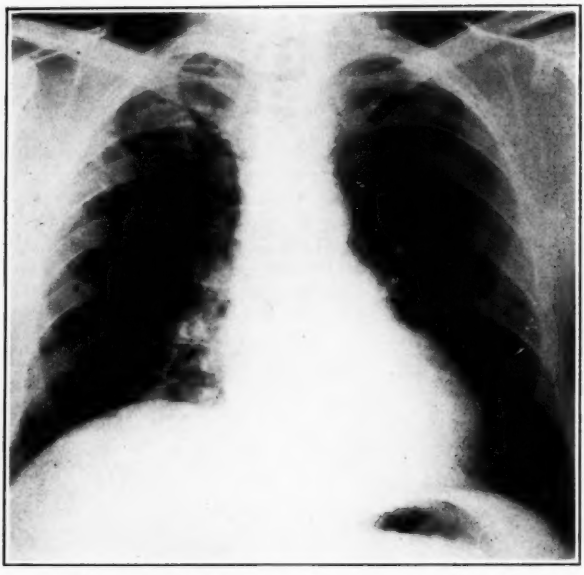

FIG. 3.—Case 3, taken 1 month after Fig. 2 showing some residue in lower portion of right upper lobe.

considerable amount of seromucoid sputum which later contained some bright red blood. The patient was hospitalized as a case of pneumonia on October 22. There was a weight loss of 30 pounds.

Physical Examination: He was flushed and only slightly toxic. He appeared to be quite comfortable in spite of a fever of 40° C. (104° F.) and a respiratory rate of 26 per minute. The tongue was coated and moderately dry. There was impaired resonance, increased tactile and vocal fremitus, high pitched breath sounds and occasional râles over the posterior portion of the right lower lobe of the lung. The spleen was not palpable.

Laboratory Data: Hemoglobin 87%, 5,250,000 erythrocytes and 6000 leukocytes, 46% of which were lymphocytes. Urine normal; blood Wassermann test negative. The sputum was mucoid, tenacious and often contained bright red blood. On repeated examinations no tubercle bacilli were found. White mice and guinea pigs failed to become infected with pneumococci or brucella following injection with sputum. Agglutination tests for brucella abortus showed complete agglutination in dilution of 1 to 2560 and partial in 1 to 5120. The Mantoux skin test was negative and skin tests with heat killed brucella gave a moderately positive reaction. Three blood cultures were negative. A Roentgen ray plate of chest taken October 31, 1933 (Fig. 1) showed a diffuse increase of bronchiovascular markings suggesting a chronic non-tuberculous lung infection and a diffuse density in the medial inferior portion of the right lung suggestive of an unresolved pneumonia. Later roentgenograms showed some extension of the lesion but no change in its character.

Although fever was present each day it gradually diminished, and the patient improved slowly. By December 15, 15 weeks after the onset of his illness and 10 weeks after the development of the pulmonary symptoms, the patient had become afebrile and was discharged with some residual pulmonary infiltration in the right lower lobe. A Roentgen ray plate taken 4 weeks later showed that resolution had occurred.

CASE 3.—E. M., male, aged 61, a caretaker of small animals experimentally infected with undulant fever, complained of generalized aches and pains on October 27, 1933. November 1, he developed spells of weakness, headache, vertigo and profuse drenching night sweats and noticed some cough which produced a seromucoid sputum. These symptoms continued to come on in the late afternoon and evening. About December 1 he thought he was catching cold and felt worse. December 8 he felt hot and had sharp lancinating pain in the upper part of the right side of the chest with backache and headache. He continued to have fever and drenching sweats but no chills. He was forced to stop working on December 9. He reported to the Dispensary December 12 where his chest was examined but no abnormal findings were recorded. A Roentgen ray picture taken at that time showed a small area of increased density in lower portion of the right upper lobe. A lateral chest plate showed this lesion to be centrally placed. He was admitted to the hospital as a case of pneumonia on December 13. In spite of a temperature of 39.2° C. (102.5° F.) the patient did not appear very ill.

Physical Examination: Several small cervical nodes were found. A few râles were heard at the level of the eighth spine posteriorly and about 2 inches to the right of the spine. The spleen was palpable, the heart showed a slight left ventricular hypertrophy. Blood pressure 190/96. Temperature 37.78° C. (100° F.), pulse rate of 100, respiration rate 24.

Laboratory Data: The urine was negative on several occasions. Hemoglobin 78%, erythrocyte count 3,500,000, leukocyte count 8170 with a normal differential cell count. Agglutination test for Brucella abortus was complete in a dilution of 1 to 160. Blood cultures were negative. Wasser-

mann reactions were negative. Skin test with heat killed brucella gave an elevated indurated reddened area 1.5 cm. in diameter after 48 hours. Guinea pigs inoculated with sputum were negative.

While the patient was in the hospital the fever varied from 37.78° C. (100° F.) to 39.7° C. (103.4° F.) with an afternoon rise for 6 days, then slowly decreased followed by several exacerbations of above 37.78° C. (100° F.) for a period of about 2 months. The leukocytes count remained normal throughout the illness. Roentgen ray plates of the chest taken December 22, (Fig. 2) showed an increase in the size of the haziness previously noted during the first week. The shadow remained constant for about 2 months and slowly subsided. On January 20, 1934, there was still some residue of the pneumonic lesion, 17 weeks after its onset (Fig. 3). The patient was discharged on January 20, with a small residue of the pulmonary lesion and an occasional afternoon fever until February 1. A Roentgen ray plate taken March 2, showed the pulmonary lesions had entirely disappeared 4 months after the onset of the pulmonary symptoms.

Comment. These cases of undulant fever, each regarded as pneumonia when first seen, illustrate the error of focusing the attention to signs and symptoms confined to the lungs. Careful history, physical examination and laboratory studies revealed the pulmonary lesion to be merely part of the general infection. The 3 cases had several features in common, namely, a period of several weeks of mild illness before the onset of pneumonic symptoms, none were very ill at any time, not as ill as one would expect with pneumonia due to other organisms. The pulmonary lesions in each were atypical, according to physical signs and Roentgen ray studies and required from 13 to 17 weeks for complete clearing. In all cases an attempt should be made to determine whether the pneumonia is due to the brucella or to the more commonly encountered organisms which invade individuals whose resistance has been reduced by the disease in question. This is often impossible to decide unless there occurs opportunity for lung puncture or necropsy study. Bacteriologic proof of the specificity of the pneumonia was not possible in our cases since all patients recovered and brucella were not cultured from the sputum. The pneumonia was considered as probably due to brucella.

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VALUE OF SERIAL ELECTROCARDIOGRAMS IN CORONARY THROMBOSIS.*

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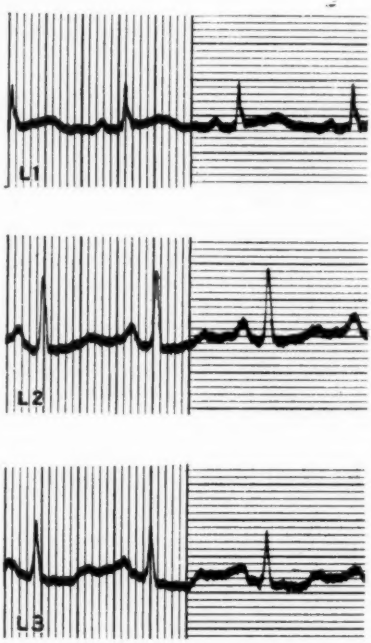
The not infrequent failure of a single electrocardiogram to show coronary thrombosis in cases having a history of a prolonged anginal syndrome, with dyspnea, epigastric distress, fall in blood pressure, fever, leukocytosis, perhaps pericardial friction and even positive autopsy findings, has unfortunately detracted from the true value of this method of examination.[1, 2, 3]

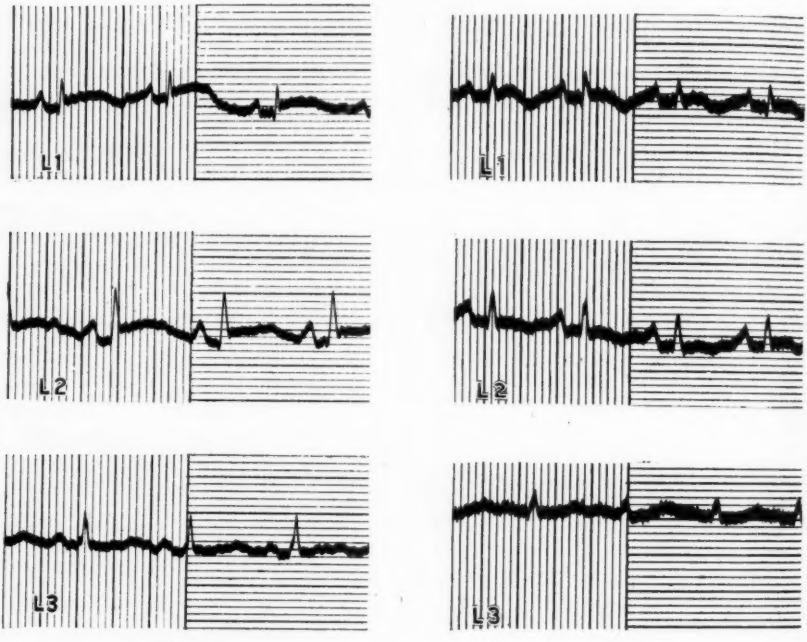


Series "A," No. 1. Twelve hours after onset of typical symptoms of coronary thrombosis, illustrating the cove-shaped T_1 with reciprocal T_3 and prominent P_2. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No, 3—between left arm and left leg.

Since a coronary accident gives rise to a series of variable changes in each individual heart, depending largely upon the degree of collateral circulation, the location and size of the occluded vessel and other factors whose relationship is less well understood, such

* Read before the 18th Annual Clinical Session of the American College of Physicians, in Chicago, April 16, 1934.

as the chemical and physical reactions of the blood and tissues, the platelet count, and so forth, so the electrocardiographic curves in turn show considerable diversification.[4, 5] When a large vessel is suddenly obstructed, with insufficient collateral circulation, we may expect an early injury current, showing *one* of the forms of the characteristic coronary curves. In other instances, where a tiny twig is occluded, with a good collateral circulation, the patient may experience a prolonged anginal syndrome without showing any



No. 2. No. 3.

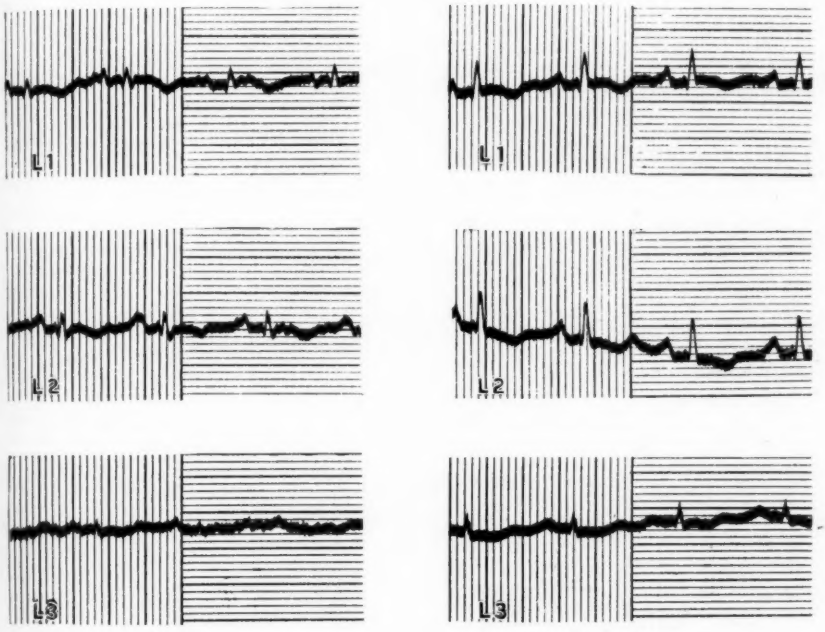
Series "A," No. 2. Two days following "A"1, showing the elevated R–T_1 and $_2$ with prominent P_2, and lowered voltage. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "A," No. 3. Twenty-six days following "A"2, showing marked decrease in voltage, with inverted T_1. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

variation in the electrocardiogram. Where a gradual thrombosis takes place, correspondingly gradual changes in the electrocardiographic records may be found, or there may be no change until the occlusion is complete, thereby giving only late variations, the characteristic curves being delayed for a week or more. In others, where the initial insult has been the occlusion of a small branch, with good collateral circulation, a positive curve may appear early and rapidly revert to normal limits. Should some of the collateral

circulation in turn be occluded, the characteristic positive form may again become manifest.

Priest and Saphir have demonstrated the autopsy findings of patients who have had coronary thrombosis without infarction who later developed infarction in the area supplied by the original occluded vessel following thrombosis of vessels supplying collateral circulation to this part.[6] As pointed out by Willius,[5, 7] and Fowler



No. 4. No. 5.

Series "A," No. 4. Fourteen days after "A"3—a further decrease in voltage, with prominent P_2 persisting. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "A," No. 5. Eleven days following "A"4, demonstrating an increase in voltage, with recovery. (The Series "A" demonstrating the changing EKG of coronary thrombosis.) Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

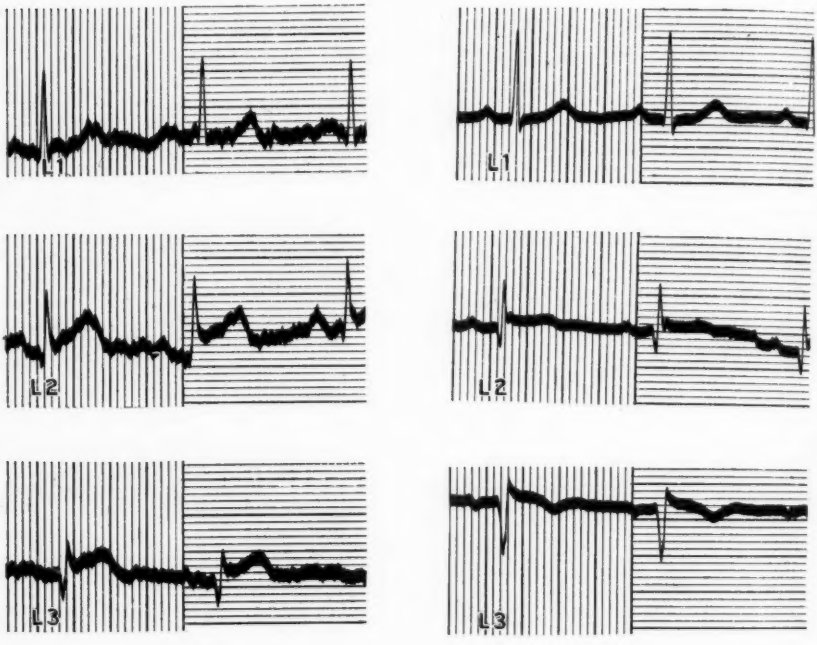
and Smith,[8] the attack may consist of a series of coronary thromboses.

And so, many conditions may alter the simple sequelæ of an obstructed coronary vessel, at times giving electrical potentials resulting in unusual and atypical curves. The most conclusive evidence is obtained by reviewing a series of electrocardiograms, keeping a watchful eye for the characteristic changes of coronary thrombosis. These signs are now well known and comprise:

(*a*) The elevation and depression of the *R–T* intervals, with at times reciprocal changes in Leads I and III.[9, 10]

(*b*) Cove-shaped Pardee *T* waves,[11] with later inversion of the terminal portion and conversely the sharply upright *T* wave the exact opposite of the "Pardee-wave," with elevation of the *R–T* interval, as described by Bohning and Katz.[12]

(*c*) The low voltage of the *Q–R–S* complexes, as emphasized by White[13] and Wearn.[14]



No. 1. No. 2.

Series "B," No. 1. Illustrating the high take-off of T_2 and 3, three hours after the onset of a coronary accident. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "B," No. 2. Twenty-four hours later, showing a decrease in the height of the *T* take-off in Leads II and III, with a flattening of T_3 and terminal inversion of T_3. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

(*d*) The deep Q_3 following the criteria of Pardee.[15]

(*e*) Prominent Q_1 and Q_2, described by Wilson and others.[16]

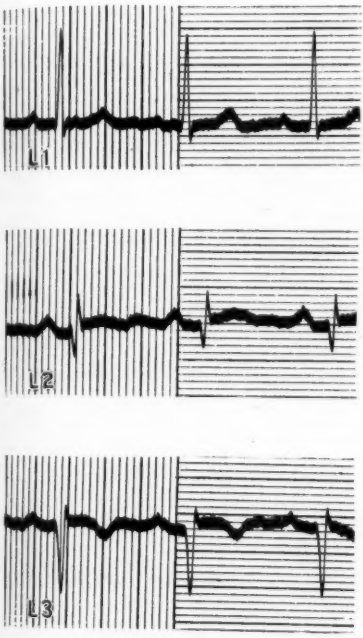
(*f*) The upright or diphasic *T* waves in the chest leads, with displaced *R–T* intervals, according to Wood *et al.*[17]

(*g*) Prominent *P* waves of Masters,[18] and

(*h*) Equally important and more constant than all the foregoing findings, variations in the serial curves themselves, as emphasized by Herrick,[4] Cooksey and Freund,[3] Oille,[19] and others.[20]

Hurxthal reports a case in which T_1 was inverted 6 days before the attack and became upright 1 hour after the accident.[1]

In reviewing a series of 72 cases where serial curves were obtained only 2 failed to show significant changes.* One occurred in a physician of 35 with typical history and findings, including pericardial friction, fever, leukocytosis, with prostration and stenocardia at the



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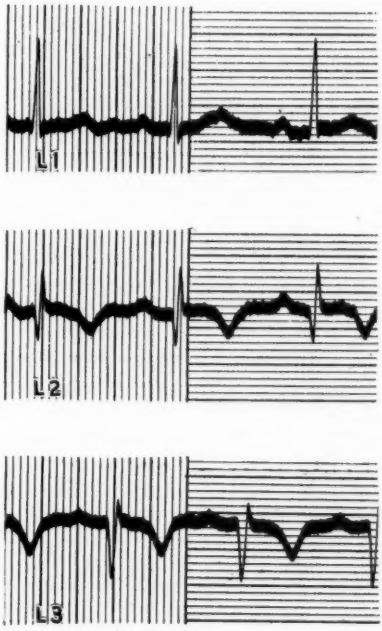


No. 4.

Series "B," No. 3. Forty-eight hours following "B"2, showing a further inversion of T_3, with R–T_2 and 3 approaching the isoelectric line. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "B," No. 4. Ten days after B_3, showing deep inversion of T_2 and 3, with slight elevation of R–T_2 and 3. (Series "B" illustrating the changing EKG of coronary thrombosis.) Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

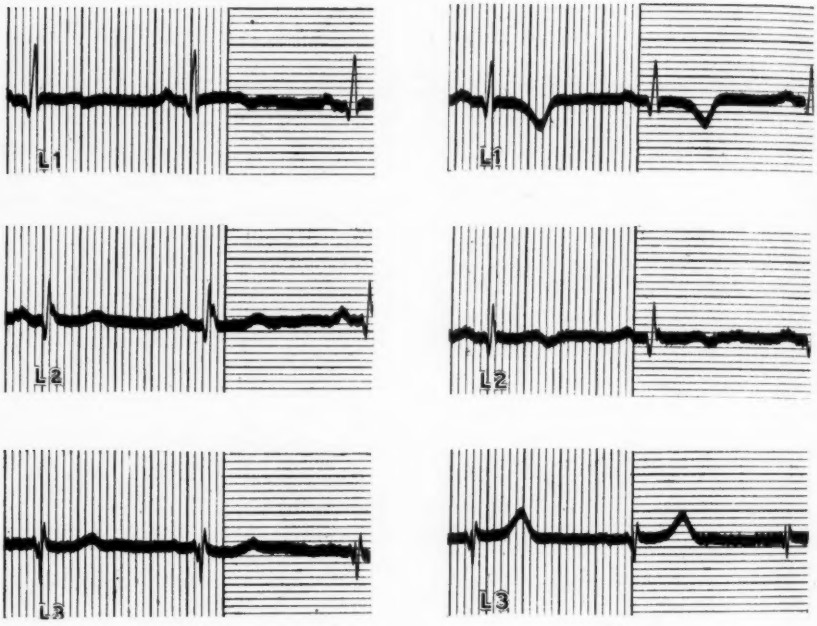
onset. The other was in a physician in the sixties, who showed only a slight flattening of the T wave. A series of 6 serial curves were obtained in the first case, over a period of 3 months, and a series of 7 in the second case, over a period of a year. So, at times, confirmatory evidence may be seen in a normal curve where the T wave was previously inverted, or there may be only a flattening or inversion of a previously upright T wave. Six cases of the present series with 3 or more serial records displayed a slight inversion of

* Records of St. Francis Hospital (Evanston), Evanston Hospital, Swedish Covenant Hospital, Chicago, and private patients.

T_1 or T_1 and T_2, occurring from the 10th to the 18th day; 3 showed changing arrhythmias, with no characteristic alteration in the T waves or R–T intervals.

Cooksey and Freund have studied 24 cases with serial curves, showing 100% positive findings.[3]

Pardee[21] reports 25 cases at the New York Hospital which had almost daily records, showing positive findings in at least one record



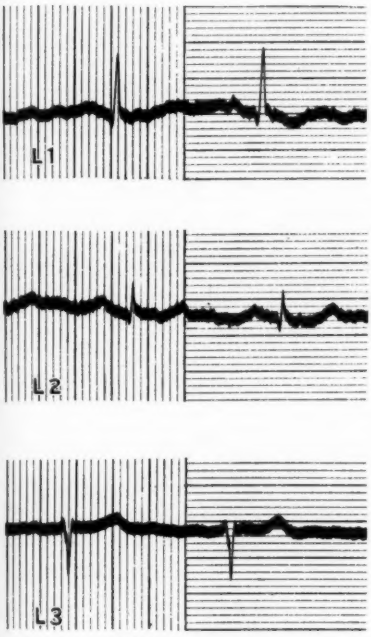
No. 1. No. 2.

Series "C," No. 1. Forty-eight hours following a coronary accident, showing prominent Q_1 and $_2$, with cove-shaped T_1, slightly increased R–T_2, and T_3 reciprocal of T_1. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "C," No. 2. Twenty days after "C"1, showing marked inversion of T_1 with reciprocal upright T_3, inversion of T_2, and decreased voltage of Q–R–S, all leads. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

in all the patients. Oille reviewed 200 cases from the records of Toronto General Hospital in which only 2 or possibly 3 showed no significant signs. He cites 2 cases which showed significant changes 2 days before the pain and clinical onset.[22] Kelly also noted a case at Cook County Hospital where a routine electrocardiogram was taken, showing positive signs of coronary occlusion, with the clinical attack of pain, cardiac failure, fever and leukocytosis occurring 24 hours later.[23]

Coronary occlusion curves may be simulated by those found in other conditions, such as chronic valvular disease, active rheumatic infection,[24] influenza,[25] diphtheria,[26] pneumonia,[27] hyperthyroidism, pericarditis with effusion, uremia, and certain drug poisonings, such as digitalis,[28] quinidin and emetin. The hearts of athletes, probably hypertrophied, but usually showing teleradiograms within normal limits, occasionally give suggestive elevations and depressions of



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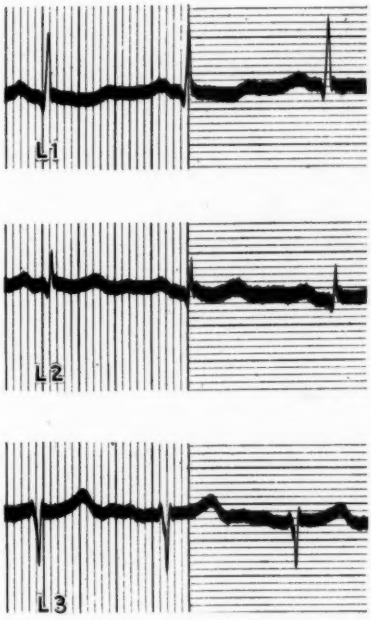


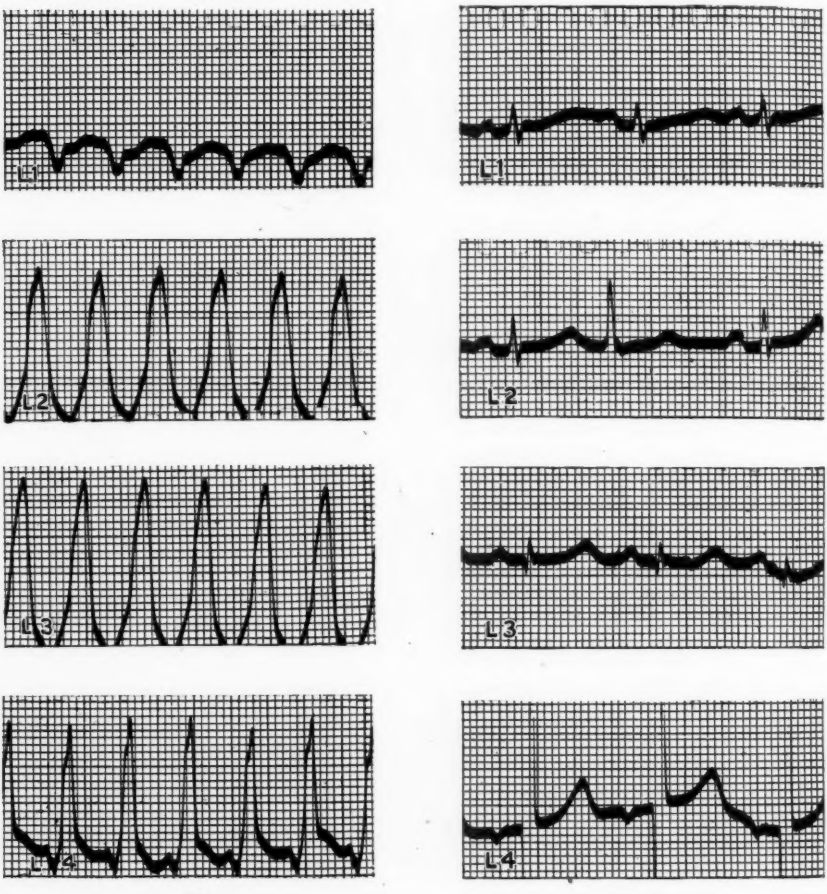
No. 5.

Series "C," No. 4. Twenty days following "C"3, showing increased voltage, with T_1 approaching the isoelectric line. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "C," No. 5. Forty-eight days following "C"4, showing practically isoelectric T_1 and decrease in the voltage of the upright T_3. (Series "C" illustrating the changing EKG of coronary thrombosis.) Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

the *R–T* intervals resembling one of the forms seen in coronary thrombosis. Some of the coronary forms have been simulated by placing the patient with a normal heart in unusual positions.[29] Serial curves in coronary thrombosis will rule out simulating curves of other conditions which are constant in form, such as those of chronic valvular disease, the hypertrophied hearts of athletes, chronic coronary disease (as the curves in coronary sclerosis), and in some cases of thyroid disease, as in the case of Dr. C., who showed

a persistent bundle-branch block for 2 years, returning to normal following the removal of a substernal thyroid tumor. In the case of active infection and drug intoxication where serial curves may show change from day to day, the findings in the coronary waves



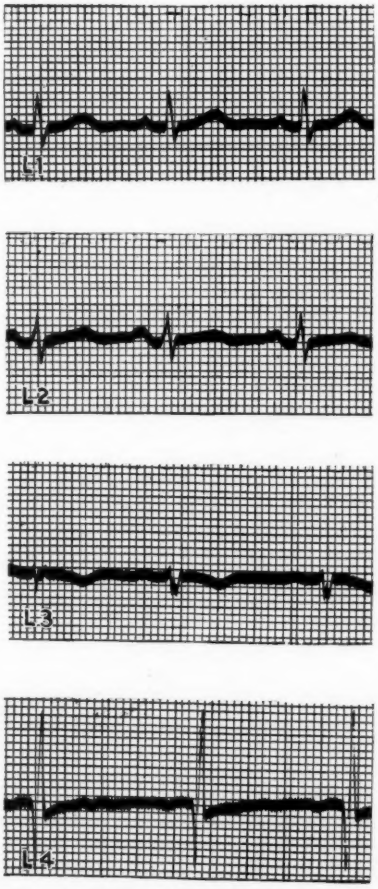
No. 1. No. 2.

Series "E," No. 1. Twelve hours after onset of thrombosis, showing ventricular tachycardia.

Series "E," No. 2. Three days following "E"1; heavy quinidin therapy, showing low voltage; nodal extrasystole Lead II, increased R–T_3 and sharply upright T_4.

are usually more characteristic and very infrequently lead to a faulty diagnosis. Careful correlation of the electrocardiogram with the clinical history and findings is, of course, always advisable and often essential.

The more frequently electrocardiograms are taken the more evidence will be obtained. From a practical standpoint it is desirable to obtain the information early and take the minimum number of records; it is suggested, therefore, that a curve be taken as soon after the accident as possible, followed by another the following



Series "E," No. 4. Showing inverted T_3, isoelectric T_4, with upright T_1 reciprocal of T_3. (The series "E" demonstrating the changing EKG of coronary thrombosis.) In Series "E," Lead IV is taken through chest with right arm electrode anterior over cardiac apex and left arm electrode posterior between angle of scapula and vertebral column.

day, with a third curve 48 hours after the second, and further curves, if necessary, at weekly intervals for a month or longer. If these serial records are obtained the accuracy of the electrocardiographic examination in coronary thrombosis will closely approach that of the Wassermann and Kahn tests in syphilis.

Summary and Conclusions. An attempt has been made to show the value of serial curves in the diagnosis of coronary thrombosis.

1. It is possible for single records to be taken at times when characteristic signs of coronary thrombosis are absent.

2. The serial records are usually characteristic and rule out those conditions simulating coronary occlusion curves in a single record, such as seen in chronic valvular disease, hypertrophied hearts of athletes, and those of chronic coronary disease.

3. The serial curves of acute infectious diseases usually are not characteristic enough to confuse the diagnosis. In an occasional case it may be necessary to rely upon the correlation of the clinical history and findings with the electrocardiogram.

4. The time of taking these curves for practical purposes has been suggested, *i. e.*, as soon as possible after the accident; then, the next day; 48 hours after the second; and, if necessary, at weekly intervals for a month or longer.

5. It may be that chest leads will further increase the accuracy of serial curves. In our experience the fourth lead has been more sensitive to digitalis than the conventional leads.

6. In 72 cases of coronary thrombosis where serial curves were taken only 2 failed to show significant changes.

7. Serial curves of 4 cases are shown.

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OBSERVATIONS ON THE EFFECT OF AN ARTERIOVENOUS FISTULA ON THE HUMAN CIRCULATION.

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An arteriovenous fistula causes profound changes in the circulation. The condition is not uncommon and its clinical characteristics are now well recognized. Adequate study, however, has been limited to relatively few cases and for that reason the mechanism of many of its effects is still controversial. Further investigation may be expected not only to clarify the phenomena associated with arteriovenous communications, but also to throw light upon related conditions in the cardiovascular system. The following observations are therefore reported which were made upon a case exhibiting the characteristic effects of a traumatic fistula between the left femoral artery and vein.

Nicoladoni[17] in 1785 first described the fact that occlusion of an arteriovenous fistula by digital compression is followed by a marked slowing of the pulse rate, the so-called bradycardiac reaction or Branham's sign.[20] Subsequent studies have shown that this is associated with a rise of arterial blood pressure upon which it is believed to depend. Other effects of such a fistula include an increase in the total blood volume, a decrease in the systemic capillary blood flow, generalized arteriolar dilatation and many of the peripheral signs of aortic regurgitation. The effect on the heart itself is the production in the majority of cases of a striking degree of enlargement. Progressive circulatory insufficiency is the rule in the presence of a fistula of significant size involving a large artery.

In the treatment of aortic aneurysm, end-to-end anastomoses have been established between artery and vein apparently without untoward effect.[1,26] Since the present case exhibited a fistula of the lateral type, the conclusions reached in this study do not necessarily apply entirely to other forms of arteriovenous communications, either surgical or congenital.[23]

Case Report. D. W., a colored male, aged 35, and a laborer by occupation, was admitted to the Philadelphia General Hospital on June 4, 1934, complaining of shortness of breath and swelling of the legs. He stated that he had been in good health until 5 months previous, at which time he had been accidentally shot, a 0.38-caliber bullet entering his left groin. He remained for 8 days in a local hospital during which time his left leg became swollen. On returning home he first noticed a buzzing sensation beneath the site of injury. He returned to work, but found that both

legs then began to swell. He was short of breath and fatigued by slight effort. The symptoms gradually increased in severity and were accompanied by attacks of faintness, palpitation and precordial pain. He became unable to sleep in a recumbent posture and awoke to urinate several times nightly. Occasionally the urine appeared red. Rest at first caused subsidence of the swelling and dyspnea, but the symptoms ultimately became so severe that he was forced to give up his work and come to the hospital. The patient was married, had no children and indulged in alcohol to excess. The family history was negative for cardiovascular renal disease and the past medical history was irrelevant.

Physical examination revealed a well-developed colored male with marked edema of both legs. The temperature was 99°, respiratory rate 20, pulse rate 80 and blood pressure 140/80. Cyanosis was not evident. The tendon and pupillary reflexes were normal. The head showed no significant abnormality. Examination of the lungs showed evidence of passive congestion. The heart was greatly enlarged to percussion, the borders being 14 cm. to the left of the midline, and 5 cm. to the right. The rhythm was regular, the sounds clear and no murmurs were heard. The liver was slightly enlarged. There was no definite ascites. In the left groin there was a scar of a bullet wound, and over the upper femoral sheath a pulsating mass about the size of a walnut could be felt. Over the mass there was a well-marked systolic thrill and a bruit which was continuous but louder during systole and transmitted down the leg. Both legs were cold and exhibited pitting edema, more marked on the left side which also had a somewhat darker color. The radial arteries were not sclerosed. The pulses were full and equal and there was slight capillary pulsation visible beneath the fingernails.

Firm digital pressure on the mass in the left groin caused a disappearance of the bruit, a rise of blood pressure from 140/80 to 170/120 and a slowing of the pulse rate from 80 to 50.

Blood count showed 100% Hb., 5,000,000 R. B. C. and 5000 W. B. C. Urinalysis and blood chemistry were normal. Blood and spinal fluid Wassermann tests were negative. Teleroentgenogram showed marked passive congestion of both lungs and a greatly enlarged heart, the transverse diameter being 19.5 cm. to a chest diameter of 30 cm. (Fig. 1*a*).

Diagnosis. Traumatic arteriovenous aneurysm of the left femoral artery and vein with secondary cardiac dilatation and congestive failure.

Course. The patient was confined to bed with no essential medication from June 4 to June 14 and thereafter allowed up at will until operation, on July 13. On June 26, fluoroscopic examination showed that the transverse diameter of the heart was reduced to 16.4 cm., which value was found again on July 6. The edema of the legs persisted, especially on the affected side, but was much reduced. It was maximal in the evening and tended to subside with rest in bed.

Operation was performed on July 13, by Dr. P. A. McCarthy. Under N_2O-ether anesthesia, an incision was made exposing the left common iliac artery and vein and the deep and superficial femoral vessels. The aneurysm was enveloped in dense scar tissue, measured approximately 1½ by ¾ in., and involved the common femoral vein with a fistula from the common femoral artery. With hemostasis obtained by tapes about the common iliac and femoral arteries and veins, the aneurysm was cut free from the artery to which it was attached for a distance of about 1 in. The fistula so disclosed measured ¼ in. in diameter. The openings in the artery and vein were closed by suture with fine silk. Removal of the tapes showed free blood flow, although the peripheral segment of the artery appeared much contracted. A layer of fascia was inserted between the artery and vein and

the wound closed. Pulsation in both the femoral and dorsalis pedis arteries was palpable.

Further Course. Except for occasional vague pains in the affected leg, there were no postoperative complications. The pulse rate remained between 70 and 100 for the first 3 days and thereafter between 60 and 80. The edema disappeared entirely from both legs. Teleroentgenogram, on August 2, showed the complete disappearance of pulmonary congestion and the transverse diameter of the heart was reduced to 12.5 cm., a value well within normal range.

The patient was discharged on August 6. From that time until his last visit, on September 18, he had no complaints other than a sensation of warmth and occasional numbness in the affected leg. The heart size remained unchanged to fluoroscopic examination. There was, however, a slight pitting edema of the affected leg where pulsation was no longer palpable in the femoral and dorsalis pedis arteries. The resting blood pressure in the arm was 130/84, with a pulse rate of 70. In the right leg the blood pressure was 150/80, with an oscillometric index of 3.5, but in the left leg the blood pressure was 85/50, with an oscillometric index of 1.5. The patient had resumed his work as a laborer.

Results. The patient was studied over a period of 6 weeks before and 8 weeks after operation. The following observations were made.

Arterial Blood Pressure. Many determinations of the resting but non-basal arterial tension measured by the usual auscultatory method gave values of 140 to 156 mm. Hg. for systolic pressure and 77 to 96 for diastolic pressure. Digital compression of the aneurysm sufficient to cause disappearance of the bruit produced a consistent rise of both the systolic and diastolic levels, the former to pressures between 150 and 190 and the latter between 115 and 130 mm. Hg. After operation systolic pressure averaged 110 to 140 and diastolic pressure 70 to 84 mm. Hg. The arterial pressure under basal conditions showed less variation, the mean values being 126/62 with the fistula open, 127/81 with the fistula occluded and 119/78 after operation.

The effect of an arterial leak with diminution of the peripheral resistance is to cause a lowering of blood pressure, most marked in diastole. In the present case, however, the non-basal blood pressure was usually higher with the fistula open than after operative closure. Under basal conditions the low diastolic level was partly compensated by an increased pulse pressure. This fact is of importance since a diminished coronary blood flow in arteriovenous fistula has been attributed to a low perfusion pressure in the aorta.[18] Actually the mean pressure remained well within what are considered to be the normal physiologic limits. As to the sudden rise of blood pressure on digital occlusion of the fistula there is no reason to suppose that it is other than a purely hemodynamic effect of an increased peripheral resistance.[7,18]

The use of an optical oscillometer permitted the estimation of both end and lateral pressures.[3] These determinations were made under basal conditions. The average difference between end and

lateral pressure in diastole did not exceed 5 mm. Hg. and was relatively negligible. The systolic end pressure, however, exceeded the corresponding lateral pressure by 17 mm. Hg. On occlusion of the fistula, both by compression and operation, this difference was reduced to 8 mm. Hg. or one-half of its former value. The phenomenon is attributable to the increase in velocity of systolic expulsion in the presence of an arterial leak. It is similar in cause to the relatively greater difference between end and lateral pressure found in the presence of aortic insufficiency where an increased proportion of the arterial pressure takes the form of kinetic energy.[2] The degree of increase in the difference between end and lateral blood pressure due to arteriovenous fistula is particularly interesting since it is on account of this lowering of the lateral pressure that surgical arteriovenous anastomosis has been used in the treatment of aortic aneurysm.

A few measurements of blood pressure were made on the femoral artery under non-basal conditions. On the normal leg the average pressure with the fistula open was 224/118, increasing to 300/170 when the fistula was compressed. In the artery below the fistula, the systolic pressure rose from 193 with the fistula open to 230 on compression. After operation, blood pressure in the normal leg approximated the brachial value at 155/80 while in the operated leg, due probably to the narrowing of the sutured artery, the pressure measured only 85/50.

Pulse Rate. The bradycardiac reaction, consisting of slowing of the pulse rate on compression of an arteriovenous fistula, was well exhibited. The average pulse rate was 70 to 100 per minute with the fistula open. Digital compression of the fistula caused a slowing of the rate to 48 to 60 with a prompt return to the former values when the pressure was withdrawn. The pulse rate after operation was significantly slower and averaged between 52 and 84.

The bradycardiac reaction may be completely abolished by full doses of atropin,[18] a procedure which was not attempted in this case because of the advanced degree of circulatory insufficiency. On account of the effect of atropin, the slowing of the pulse rate on occlusion of the fistula is believed to be dependent upon the coincident rise in blood pressure.[14,18] It is interesting to note, therefore, that the degree of bradycardia is not always proportional to the change in blood pressure. An example will suffice. On one occasion compression of the fistula caused a rise of blood pressure from 144/80 to 160/120 and the pulse rate slowed from 80 to 50. With release of compression, blood pressure fell to its former level while the pulse rate increased to 84. On a second occasion compression of the fistula caused a rise of blood pressure from 110/65 to only 125/82 while the pulse rate again fell from 82 to 50. On release of compression the systolic pressure remained unchanged while the diastolic level dropped only 10 mm. Hg. to 72. Even this slight

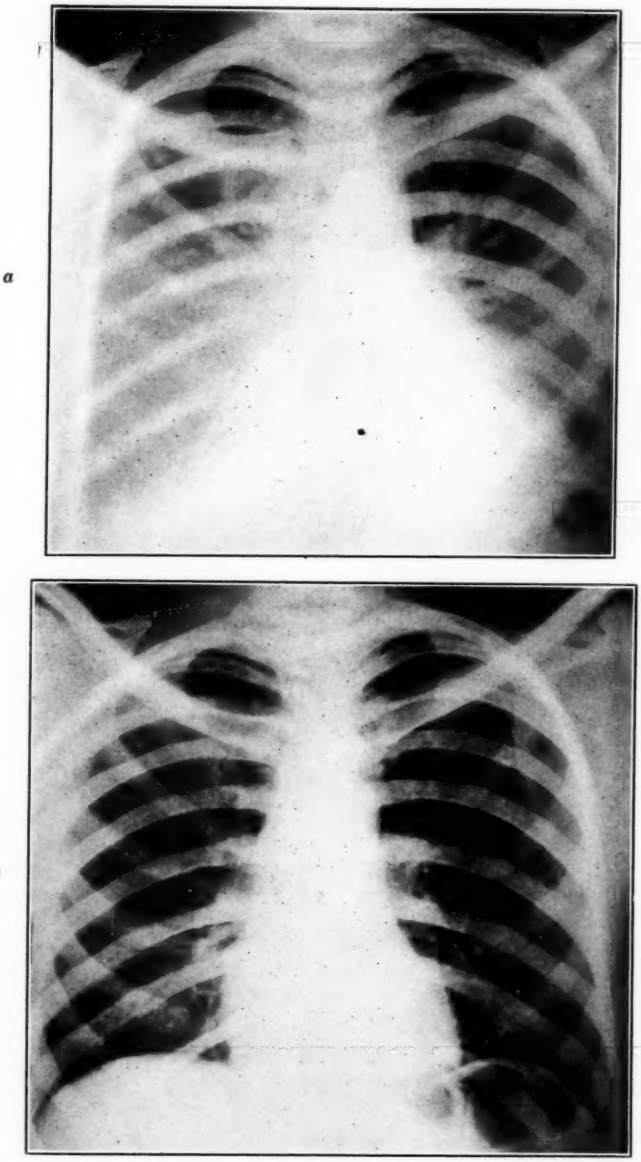

FIG. 1.—Teleroentgenogram of heart; *a*, taken 6 months after establishment of traumatic arteriovenous fistula; *b*, taken 3 weeks after operative obliteration of the fistula.

change in blood pressure, however, was accompanied by the usual increase in pulse rate from 54 to 82. In other words, equal degrees of change in pulse rate were associated with widely different degrees of change in blood pressure. Such evidence may be interpreted as indicating that the bradycardiac reaction does not depend exclusively upon the absolute height of the blood pressure, but is modified as well by other factors, including the cardiac output.

Venous Pressure. The venous pressure was not determined on admission but the degree of pulmonary congestion and peripheral edema at that time indicate that it was probably above normal. Prior to operation when the signs of congestive failure had largely disappeared, measurements of venous pressure were made by direct cannulation of the antecubital vein. Blood rose in an L tube to an average height of 75 mm. above the estimated heart level.[6] When the column of blood reached a constant level, digital compression of the fistula caused an average fall of 13 mm. After operation, the venous pressure, similarly measured, averaged 55 mm. above heart level.

It is often stated that the venous pressure is abnormally high in the presence of an arteriovenous fistula.[20] Lewis and Drury believe that in the absence of congestive failure this is not necessarily or even customarily true.[18] Observations on the present case indicate that the pressure in the peripheral veins was not above normal limits but was relatively increased by the fistula. It is questionable whether the observed pressure changes correspond exactly to changes in the right auricular pressure. If they do, the slightly higher value with the fistula open may depend upon an increase in the total venous return flow. On the other hand, the pressure in the brachial veins may not present quantitatively the values in other parts of the venous system. In any event, the alteration in venous pressure at the right auricle must have been relatively slight.

Respiration. The average respiratory minute volume at rest was 7.8 liters with a respiratory rate of 18 per minute. On compression of the fistula, these values fell to 7.3 and 17 and after operation to 6 and 16 respectively. The increased respiration probably depends upon a slowing of cerebral blood flow, but the change is seldom conspicuous.[18,24]

Skin Temperature. Estimations of skin temperature were made with a thermocouple and readings were obtained from the thigh, calf, dorsum of the foot and second toe of both legs. The average temperature was slightly higher in the leg having the aneurysm than in the normal leg, a phenomenon previously recognized.[5,14,16] On compression of the aneurysm for 10 minutes there was a rise of temperature in both legs which was greater on the normal side. The maximum rise was 0.85° C. in the affected leg and 1.45° in the normal leg.

Changes in skin temperature are probably not directly proportional to changes in total blood flow, but the values obtained indicate at least that there was a definite increase in capillary circulation through both legs when the fistula was occluded. They confirm other evidence that in the presence of arteriovenous fistula, the blood flow may be considerably diminished even in regions distant from the lesion and even in the presence of a compensatory increase in cardiac output.

Cardiac Output. The cardiac output was measured under basal conditions by the modified ethyl iodid method[25] and by the acetylene method. With the fistula open the minute volume averaged 5.15 liters making a cardiac index of 2.64. A reduction of 20% occurred on compression of the fistula, the minute volume falling to 4.13 liters and the cardiac index to 2.12. After operation the minute volume fell to 3.91 liters and the cardiac index to 2.02, making a total reduction of 24%.

The output of the heart per beat (calculated from the minute volume) averaged 65.7 cc. at a pulse rate of 78. On compression of the fistula the output per beat increased to 75.8 cc. with slowing of the pulse rate to 53. After operation the average output per beat was 68.5 cc. at a pulse rate of 56.

An increased minute volume in the presence of an arteriovenous fistula has been reported clinically[5,15,24] and in the experimental animal.[9,10,11,19] Although Lewis and Drury[18] conclude that in arteriovenous fistula "the output of the heart does not appear to be usually altered," the present case supports the clinical and experimental evidence that an increased minute volume is a compensatory mechanism of great constancy whenever the leak is of significant size and the heart is still sufficiently competent. The changes in stroke volume in clinical cases reported elsewhere in the literature are variable. In the case reported by Smith[24] there was a reduction of 65% after operation, while Ellis and Weiss[5] found, as in the present case, very little change after operation but a significant increase as an immediate effect of occlusion. The increased minute volume appears, therefore, to depend largely upon an increased pulse rate rather than upon changes in stroke volume.

Heart Size. Teleroentgenogram on admission showed an advanced degree of pulmonary congestion and a hugely enlarged heart (Fig. 1*a*) the silhouette of which measured 194 sq. cm. with a transverse diameter of 19.5 cm. The heart to chest ratio was 65%. Four weeks later, 10 days before operation, the area of the silhouette by orthodiagram had decreased to 141 sq. cm. and the transverse diameter to 16.4 cm. The patient had received no digitalis or other significant medication so that the change is presumably an effect of rest alone. Three weeks after operation the cardiac silhouette by orthodiagram measured 108 sq. cm. and the transverse diameter 12. 5 cm. with a heart to chest ratio of 42% (Fig. 1*b*). No further

change has been noted on subsequent examinations. The total reduction of the cardiac silhouette and transverse diameter was 45%.

On fluoroscopic examination prior to operation it was found that digital occlusion of the fistula caused a decrease in size of the heart shadow from 141 sq. cm. to 126 sq. cm. and of the transverse diameter from 16.4 cm. to 15.2 cm. Other observers have reported either increase[5] or decrease[22] in heart size under similar circumstances. It seems likely that the direction of change is inconstant since it is a resultant of several variable factors including venous return, heart rate, arterial blood pressure and the degree of cardiac dilatation already present.

Pulmonary Blood Volume. A phenomenon which does not appear to have been previously described is the visible change in pulmonary blood volume incident to sudden opening and closing of the fistula. Under fluoroscopic examination, digital compression of the aneurysm was followed by a prompt and consistent increase in translucency of the lung fields which diminished on reopening of the leak. The procedure was repeated and the effect confirmed by several observers. The change in translucency of the lung fields may be explained by a change in pulmonary blood volume on sudden diminution of the venous return. It probably represents a shift of blood from the venous and pulmonary bed to parts of the arterial and capillary system inadequately filled because of the short circuit at the fistula. The observation is of particular interest in view of the unexplained lowering of pulmonary resistance found by Gibbon and Churchill[9] in experimental arteriovenous fistula. It also affords further evidence of the blood reservoir function of the lungs to which Hochrein and Keller[13] have recently called attention.

Oxygen Consumption. The oxygen consumption averaged 247 cc. per minute on repeated determinations before operation, both with the fistula opened and closed. The basal metabolic rate was −8.1%. After operation the oxygen consumption was 265.7 cc. per minute or 0.5% of the calculated value. The change is too slight to be of definite significance unless it be interpreted as indicating that the oxygen consumption diminished in response to a decrease in peripheral blood flow.

Pulse-wave Velocity. The results of determinations of pulse-wave velocity from the heart to subclavian artery, subclavian to brachial and femoral arteries and femoral to dorsalis pedis arteries will be found in the table. The values estimated were at no time outside the normal range. The effect of compression of the fistula was to increase the pulse-wave velocity in the arch of the aorta and peripheral vessels and to slow it in the aortic trunk. After operative closure of the fistula the pulse-wave velocity was accelerated through all parts of the vascular system except the aortic arch. It has been stated that an arteriovenous fistula causes slowing of the pulse-wave velocity[18] but the observations in the present case indicate

that this does not necessarily apply to all parts of the arterial system since the opposite effect may occur in individual sections.

TABLE 1.—DATA ON CASE OF ARTERIOVENOUS FISTULA.

			Fistula open.	Fistula compressed.	After operation.
Pulse rate (per minute)			70–100	48–60	52–84
Arterial pressure (in mm. Hg):					
Auscultatory:	Non-basal:	Systolic	140–156	150–190	110–140
		Diastolic	77–96	115–130	70–84
	Basal:	Systolic	126	127	119
		Diastolic	62	81	78
Oscillometric:	Basal:	End systolic	129	131	123
		Lateral systolic	112	122	115
		End diastolic	65	86	81
		Lateral diastolic	62	81	78
		End to lateral systolic diff.	17	9	8
Venous pressure (corrected, in mm. blood)			75	62	55
Respiratory rate (average per minute)			18	17	16
Respiratory minute volume (in liters)			7.8	7.3	6.0
Oxygen consumption (in cc. per min.)			247.0	247.0	265.7
Basal metabolic rate			−8.1	−8.1	−0.5
Pulse-wave velocity (in meters per sec.):					
Heart to subclavian artery			3.17	3.95	2.70
Subclavian to brachial artery			5.78	5.48	7.43
Subclavian to femoral artery			4.76	4.00	5.56
Femoral to dorsalis pedis artery			8.49	9.25	10.36
Skin temperature (in ° C.):					
Average for normal leg			34.00	34.88	
Average for affected leg			34.08	34.77	
Maximum rise, normal leg			..	1.45	
Maximum rise, affected leg			..	0.85	
Cardiac output per minute:					
Acetylene			..	4.26	4.07
Ethyl iodid			5.48	3.80	3.85
			5.08	4.32	3.81
			4.90		
Average in liters per min.			5.15	4.13	3.91
Cardiac index			2.64	2.12	2.02
Decrease in cardiac output, per cent			..	−20	−24
Cardiac output per beat			68.3 (80)	73.1 (52)	68.8 (56)
(corresponding pulse rates in brackets)			66.9 (76)	78.5 (55)	68.1 (56)
			62.0 (79)		
Average in cc. per min.			65.7	75.8	68.5
Heart size, area in sq. cm. of cardiac silhouette			194		
			141	126	108
Transverse diameter in cm.			19.5		
			16.4	15.2	12.5

Electrocardiogram. In the presence of the open fistula the electrocardiogram showed a normal sinus rhythm with a rate of 120 per minute. The only abnormalities noted were a Q wave in Lead III, a flat T wave in Lead I, and a diphasic T wave in Lead IV. Digital compression of the fistula had no effect on the record other than a slowing of the rate to 80. The electrocardiogram was repeated approximately 3 weeks after operation and showed a pulse rate of 100. There was an increased amplitude of the initial ventricular complexes in all leads, the T wave in Lead I was still flat, the Q

wave in Lead III had disappeared and the T wave in Lead IV had become deeply negative.

It is rather surprising that so few signs of myocardial disturbance were found in a heart so severely affected. The absence of marked change in the form of the waves on occlusion of the fistula is also of interest and agrees with the reports of other observers.[5, 8, 22] The change in Q_3 and T_4, however, is indicative of definite improvement in the state of the myocardium after operation.

Discussion. The most important effect of an arteriovenous fistula is the remarkable degree of cardiac enlargement and its consequent circulatory insufficiency. The enlargement has been attributed to hypertrophy[7, 10, 12, 14, 21] and dilatation [14, 21, 20] due to the increased cardiac output and blood volume. That hypertrophy was not a significant factor in the present case is indicated by the rapid reduction in size of the heart after operation. Dilatation, therefore, appears to be the chief cause of the enlargement. However, it is difficult to explain so great a degree of dilatation by an increased output of only 24%, especially since aortic insufficiency associated with a comparable leak produces mainly hypertrophy. Nor is the increased blood volume likely to be an important factor as polycythemia very seldom causes a similar degree of enlargement.

Skin temperature and plethysmographic studies have indicated that occlusion of the fistula causes an increase in the peripheral capillary circulation even though the cardiac output is simultaneously diminished. Since coronary blood flow may safely be assumed to bear a proportional relationship to the peripheral circulation, it is clear that an arteriovenous fistula must produce a disproportion between work of the heart and the blood supply to the myocardium, the former being increased while the latter is relatively diminished. Lewis and Drury have therefore, suggested that the dilatation is "due to a deficient nutrition of the heart muscle consequent on the fall of mean arterial pressure," an explanation which seems to be the most likely one.

It is unnecessary, however, to postulate a fall of mean arterial pressure as the cause of an inadequate coronary blood flow. In the present case the mean blood pressure was well within normal limits and in fact was highest during periods of activity when the greatest degree of circulatory insufficiency occurred. The coronary blood flow is inadequate only because, although possibly normal in absolute quantity, it is below normal in proportion to the work of the heart. Under the circumstances, the myocardium may assume an increasingly hypodynamic state with resultant dilatation and congestive failure.

In the light of the present treatment of cardiac failure by ablation of the thyroid, these observations are very suggestive. They illustrate the fact that in cases of relative coronary insufficiency, a reduction of the disproportion between the work of the heart and

the coronary blood flow not only benefits peripheral congestion, but improves the function of the myocardium as well. This effect was exhibited when surgical repair of the arteriovenous fistula caused the disappearance of cardiac dilatation. In cases of coronary insufficiency due to organic changes, ablation of the thyroid similarly reduces the work of the heart to meet the limitations of the coronary blood flow. The favorable effect of this procedure depends in part upon the reduction of the body requirement for a normal minute volume. It may also depend, however, on the fact that the nutrition of the heart becomes adequate with a resultant decrease in cardiac dilatation in many cases and a definite improvement in myocardial function as exhibited by an increase in exercise tolerance.[4]

Summary and Conclusions. 1. A case of traumatic femoral arteriovenous fistula is reported together with observations made with the fistula open, during external compression of the fistula and after successful surgical repair. Significant changes in the cardiovascular system are described.

2. The inconstant relationship between the characteristic rise of blood pressure and slowing of the pulse rate on occlusion of the fistula leads to the conclusion that the bradycardiac reaction is not due exclusively to blood pressure changes.

3. The basal minute volume of the heart was increased 24% by the fistula but even in the presence of the increased output there was evidence of a relatively diminished capillary blood flow.

4. In the standing posture compression of the fistula caused a conspicuous increase in translucency of the lung fields as seen fluoroscopically, indicating a marked decrease in the blood content of the lungs.

5. The area of the silhouette and the transverse diameter of the heart were reduced by 45% following treatment. It is concluded that the cardiac enlargement was due, as Lewis and Drury suggest, to a relatively inadequate coronary blood flow.

6. It is suggested that total ablation of the thyroid in cases of coronary insufficiency may be of direct benefit to cardiac function in a manner analogous to the effect of closure of an arteriovenous fistula.

Appreciation is expressed to Dr. R. G. Torrey for much helpful criticism, to Drs. I. Starr, J. Donal and J. Scott for the measurement of the cardiac output and to Dr. B. McGlone for the estimation of the skin temperature.

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STUDIES ON THE STRUCTURE AND FUNCTION OF BONE MARROW.

IV. Bone Marrow in Agranulocytosis.

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Changes* in the blood-forming organs as described in the numerous case reports of agranulocytosis have been inconsistent to a remarkable degree. On the contrary the bone marrow of 11 cases studied during the past 4 years, carefully selected as regards the clinical aspect, presented fairly constant histopathological appearances, evidenced by the fact that twice I was able to suggest the diagnosis from examination of marrow sections alone. Certain characteristic findings were barely mentioned in another article[3] and in a personal communication quoted by Strumia.[4]

In each of the first 3 articles of this series[1,2,3] I pointed out the need for meticulous care in the examination of the bone marrow, necessitated by its wide distribution and by the variability of the tissue in different bones at different ages. It was made clear: (1) That an examination based on marrow removed from but one locus

* The reader is referred to the recent article of Jackson and Parker (New England J. Med., **212**, 137, 1935), an able and probably the best survey of agranulocytosis.

was woefully inadequate; (2) that the tibial and femoral shafts could be regarded as representative of long bones with marrow normally fatty in the adult, the vertebræ, sternum and ribs of cancellous bone marrow normally cellular; (3) that, in any case, at least the femur and tibia as well as sternum (or vertebra) must be examined; (4) that the technique employed in the cutting and staining of sections must be of such quality that accurate cell identification is possible; (5) that smears *alone* are nearly valueless, in that the relative proportion of cells and their relationship one to another cannot be determined. Discrepancies in pathologic examinations have served to cloud the issue regarding the true nature of the disease process.

I cannot help remarking, however, that blame for much of the confusion concerning agranulocytosis rests with the clinician and the "blood stream hematologist" who have grasped at the findings of mucosal ulceration and profound neutropenia as the basis for diagnosis in so many of the reported cases. Would these same authors group together all instances of suppuration and leukocytosis? Their diagnoses can often be negated by a glance over clinical records. The more careful observers do not admit severe anemia, thrombocytopenia, hemorrhagic phenomena, splenomegaly, lymph-node enlargement and positive blood cultures of pathogens into the symptom complex of this disease; again, the history of administration of arsenicals, of exposure to benzol compounds, radium and Roentgen ray definitely catalogues various cases as secondary agranulocytosis. This would indicate that cases of aleukemic leukoses, aplastic anemia, known toxic and infectious suppression of the bone marrow have been indiscriminately classed with the idiopathic condition under discussion, *i. e.*, the *disease* agranulocytosis.

Concerning the relation of amidopyrin certain reports have indicated a positive etiologic status. A negative statement may be of some value. In the Philadelphia General Hospital (a year's admissions, 29,488; deaths, 4027) the approximate consumption of amidopyrin in 1934 was 120,000 tablets, yet not a single case of true agranulocytosis appeared in the 1926 necropsies performed during the year (neither were there instances on the clinical services with recovery). The few diagnoses of agranulocytosis that have been made in the hospital were proven by sternal biopsy or necropsy to be aleukemic myelosis (1 case), aleukemic lymphadenosis (1 case), aleukemic reticulosis (1 case), aplastic anemia (2 cases) and arsphenamin neutropenia (1 case, history obtained after biopsy ruled out agranulocytosis).

The 11 cases upon which the following bone marrow description is based conformed satisfactorily to the accepted hematologic and clinical pictures; they presented either acute progressive or chronic continuous profound neutropenia, relative lymphocytosis (actual lymphopenia), no anemia or thrombocytopenia of consequence, no

hemorrhagic phenomena; necrotizing mucosal lesions were more or less prominent and 1 case gave a history of remission and relapse. Possibilities of aleukemic leukoses, aplastic anemia, leukotoxins (other than amidopyrin and allied drugs in some instances), septic and irradiation neutropenia were completely excluded. The duration of illness varied from 3 days to more than 10 months. Sufficient similarity in the essential histopathologic changes exists to allow individual protocols to be omitted in favor of a general survey.

TABLE 1.—SUMMARY OF CLINICAL DATA.

Case No.	Aut. No.	Age	Sex	Duration of disease	Type	Leukocytes, range, thousands.	Neutrophils, range %	Erythrocytes, range, millions.
1	UH-27-14	48	F	1 wk.	Acute	0.6-0.5	0-0	4.4-4.4
2	UH-30-18	31	F	10 dys.	Acute	1.0-0.8	0-0	4.8-4.6
3	UH-31-22	56	M	1 wk.	Acute	1.2-0.5	0-0	4.4-3.3
4	UH-31-191	23	F	9 mos. 3 dys.	Chr. remit. Ac. termin.	3.0-1.9	7-0	4.8-4.8
5	UH-31-498	78	M	3 wks.	Acute	2.1-1.5	16-0	3.9-3.1
6	UH-31-513	58	F	1 wk.	Acute*	1.0-0.2	0-0	4.8-4.3
7	UH-31-886	52	M	3 dys.	Acute	5.0-5.0	0-0	3.6-3.5
8	UH-31-943	61	M	10 mos.	Chr. contin.	3.2-1.9	16-0	4.5-2.6
9	UH-32-138	19	M	4½ mos.	Chr. contin.	16.3-1.5	33-0	4.6-2.4
10	PH-32-62	50	F	10 mos.+	Chr. contin.	2.6-0.66	6-0	5.5-2.9
11	LH-982	?	M	6 dys.	Acute	1.7-0.5	10-2	3.7-3.2

* Possible previous attack.

NOTE.—Cases 1, 2, 3, 5, 6, 7, 8 and 9 were used in a previous paper by Fitz-Hugh and Comroe (AM. J. MED. SCI., **185**, 552, 1933), the pathologic material utilized here through their courtesy. I am indebted to Drs. Klein and Fowler of the Presbyterian Hospital for Case 10, and to Dr. Brown of the Lankenau Hospital for Case 11.

Gross description hardly justifies the effort. Soft to semifluid marrow, seemingly degenerated, may show nice preservation of cell structure; red marrow in the femur may be simple congested fat; yellow-gray marrow may be largely cellular; firm red marrow may be badly degenerated. Attention then is given here only to the microscopic picture.

Degree of cellularity varies considerably in different bones of individual cases but the qualitative changes are similar. The femur is found to be a good barometer of marrow activity, hyperplasia being roughly in direct proportion to the duration of illness; two exceptions are noted later. The earliest changes are found in the femur of Case 4 (Plate I), an instance of recurrent agranulocytosis with a terminal relapse of but 3 days' duration. The most marked hyperplasia exists in Case 10, the patient having been constantly neutropenic (600 to 2600) for over 10 months (Plate II, upper and middle). The differential cell count (1000 cells each) in these two marrows compared with the normal and two types of secondary

agranulocytosis affords an interesting basis for description and discussion.

TABLE 2.—DIFFERENTIAL MARROW COUNTS (PER CENTS).
(*Azure II—Eosin.*) (1000 cells each.)

	Normal.*	Agranulocytosis.		Arsphen. neutropenia.	Septic neutropenia.
		Early changes (Case 4).	Marked changes (Case 10).		
Granulocyte series:					
Myeloblasts	0.6	37.3	45.1	6.6	3.6
Promyelocytes	9.0	2.6	9.5	8.2	6.0
Myelocytes (neutrophil)	34.6	0.2	1.2	29.2	18.8
Myelocytes (eosinophil)	2.0	0.1	2.5	2.2	1.2
Myelocytes (basophil)	0.0	0.0	0.4	0.0	0.0
Metamyelocytes† (neutrophil)	14.6	0.0	0.6	16.2	15.6
Segmented forms (all types)	3.0‡	0.0	0.0	5.0	26.2
Erythrocyte series:					
Megaloblasts	0.0	3.5	0.5	1.0	0.2
Erythroblasts	14.8	19.2	6.5	14.4	9.2
Normoblasts	18.2	19.9	10.4	10.8	10.4
Thrombocyte series:					
Megakaryoblasts	0.2	1.2	1.4	1.2	0.2
Megakaryocytes	0.8	1.4	2.1	1.2	0.6
Reticulo-endothelial apparatus:					
Reticular forms	2.0	7.9	3.4	3.8	3.2
Wandering forms	0.2	1.2	1.3	0.0	3.8
Lymphatic series:					
Lymphocytes	0.0	4.2	11.6	0.2	0.8
Plasmacytes	0.0	1.3	3.5	0.0	0.2

(Dense folliculoid accumulations of lymphocytes were avoided in agranulocytosis cases.)

* Case of brain tumor (white female, aged 22) with normal leukocyte count.

† Metamyelocytes include all cells between myelocyte and segmented form for simplification.

‡ This figure is lower than usual.

In early hyperplasia of fatty marrow, cells of the general reticulum tend to assume certain morphologic characters of the myeloblasts while still retaining cytoplasmic processes in relation to reticular fibrillæ. Marked proliferative activity of myeloblasts is usually prominent, evidenced by the frequent appearance of mitotic figures, occasionally to a degree suggestive of myelosis; unlike myelosis, however, it does not proceed at the expense of the other marrow elements and never results in the so-called "replacement anemia" (profound, progressive anemia and thrombocytopenia). Most myeloblasts appear normal in all respects; some, however, show vacuolated cytoplasm, frayed cell margin and a nucleus sometimes shrunken and pyknotic, sometimes faded to the extent that a thin rim of chromatin marks the line of the perinuclear membrane. Acquisition of granules is preceded by the appearance of a lighter blue zone near the nucleus, usually eccentric; granules of the pro-

myelocyte are usually sparser than one finds in the normally developing cell and are occasionally polychromatic. The apparently fully granulated myelocyte may be entirely normal but one often finds the granules loosely arranged and the cytoplasmic edge ragged. The latter changes are seen in the metamyelocyte as well; these cells have been found occasionally quite agranular. Segmented forms are seen so rarely as to be negligible. In the normal individual the neutrophilic level of the blood is maintained by a marrow containing but few myeloblasts, proliferation of promyelocytes and myelocytes at an unhurried rate being quite adequate. In agranulocytosis we have a superabundance of the early progenitors of the neutrophilic leukocyte and an extreme paucity of more mature forms.

Eosinophils usually appear structurally normal, sometimes with swollen granules and are encountered nearly always in the promyelocyte or myelocyte stage; percentage varies in the individual case but seems to bear no relation to the duration of the disease. Basophils have been seen in a few instances and are regarded as of no significance.

Erythropoiesis is in all instances of the normoblastic type, the occasional appearance of megaloblasts apparently indicating hyperactivity of moderate degree, and they are noted mostly in early hyperplasia of fatty marrow. In such instances the hemopoietic capillaries described by Doan in the rabbit and Peabody in man are demonstrable. Cell morphology in this series shows no change, except for a few binuclear erythroblasts in foci of active proliferation.

The usual degenerative-regenerative balance of megakaryocytes that one finds in the normal marrow is maintained here, augmented by a greater percentage of megakaryoblasts. The marked degeneration in this cell type described by some authors has not been observed in my series.

In addition to the scattering of lymphocytes and plasmocytes throughout the marrow dense focal accumulations occur, sometimes with a loose center and closely packed rim, so that, when viewed with the low-power objective, they may appear as typical follicles. Close examination of the central portions of such lymphoid masses, however, reveals considerable numbers of large faded cells in the background; I have wondered whether they are truly lymph follicles or merely folliculoid accumulations in response to focal degeneration. They have been observed more or less distinctly in 9 of the 11 cases; such aggregations are exceedingly infrequent findings in a given series of marrows from other types of disease. Plasmocytes are often large and multinucleated, and a few Russell body cells are encountered.

The exceptional Cases 6 and 11, ill 6 and 7 days, respectively, showed a relatively hypoplastic marrow, although general qualitative changes were those already mentioned; the femur in Case 11

was entirely fatty. Cellular degeneration exceeded that of the other cases of the series (Plate III, lower), amounting in some areas to actual necrosis, with disintegrating cells lying in the background of fibrin and edematous fluid; even here the granulocyte group suffered more damage than the other cell elements.

To summarize the marrow picture, one's attention is drawn to the progenitors of the neutrophil which are conspicuous both in number and especially through the absence of granulated forms, myeloblasts representing nearly the entire group. In the early hyperplasia of the long bones the proportion of these cells to the erythrocyte series is considerably less than that in normal marrow, the two lines of cells starting from scratch, as it were. In chronic cases, however, the myeloblasts surge far ahead while erythroblastic proliferation pursues a comparatively even course or perhaps even regresses somewhat. Activity of the cells of the general reticulum is more apparent early, as well.

LEGENDS FOR PLATES I, II AND III.

KEY

ADV	—adventitial cell (Marchand)	MBL	—myeloblast
BT	—bone trabecula	MGBL	—megaloblast
END	—endothelial cell	MKBL	—megakaryoblast
ERBL	—erythroblast	MKC	—megakaryocyte
ERC	—erythrocyte	MLC	—myelocyte
F	—fibrin	NBL	—normoblast
FC	—fat cell	PL	—plasmocyte
L	—lymphocyte		

All sections stained by modification of Maximow's azure II eosin: tissue shown in Plate I, Plate II (lower) and Plate III (upper) sectioned in celloidin, others in paraffin; photomicrographs with Leitz apochromatic optical system (red filter with Wratten and Wainwright M plates).

PLATE I.—*Upper.* Early hyperplasia of myeloblasts and erythroblasts at midfemur with focal accumulation of lymphocytes (L) (× 70) (Case 4).

Middle. Same; proliferation of myeloblasts in marrow interstices with admixture of a few cells of the erythropoietic series (× 690).

Lower. Same; focus of normal erythropoiesis accompanied by new formation of megakaryocytes (× 690).

PLATE II.—*Upper.* Marked hyperplasia at midfemur, the predominant cells being the pale-staining myeloblasts; the center (L) is a folliculoid accumulation of lymphocytes: the strands of dark cells in the periphery are clumps of late erythroblasts and normoblasts (× 40) (Case 10).

Middle. High power of above shows the majority of cells to be myeloblasts, a single myelocyte, a few lymphocytes and normoblasts and a plasmocyte being admixed (× 690).

Lower. Myeloblastic proliferation in vertebra, none being differentiated beyond promyelocyte stage; a focus of normal erythropoiesis is seen in the lower left (× 550) (Case 2).

PLATE III.—*Upper.* Area of focal necrosis in vertebral marrow with pseudofollicular aggregation of lymphocytes; cells in the periphery are largely myeloblasts (× 70) (Case 2).

Lower. Late degeneration of myeloblasts in a background of fibrin and cell débris (vertebra); the intermingled normoblasts do not share the degeneration (× 690) (Case 11).

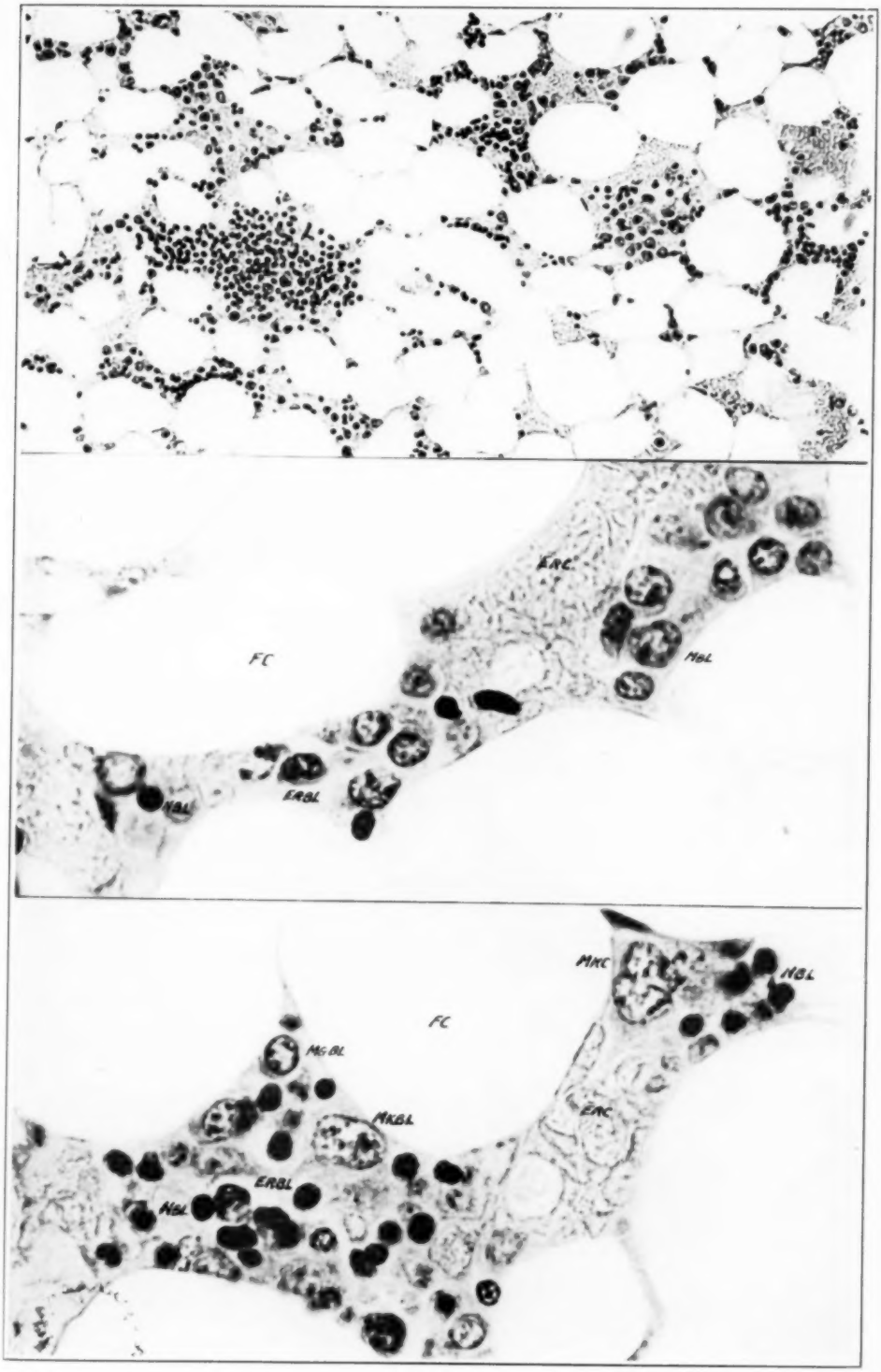

PLATE I.

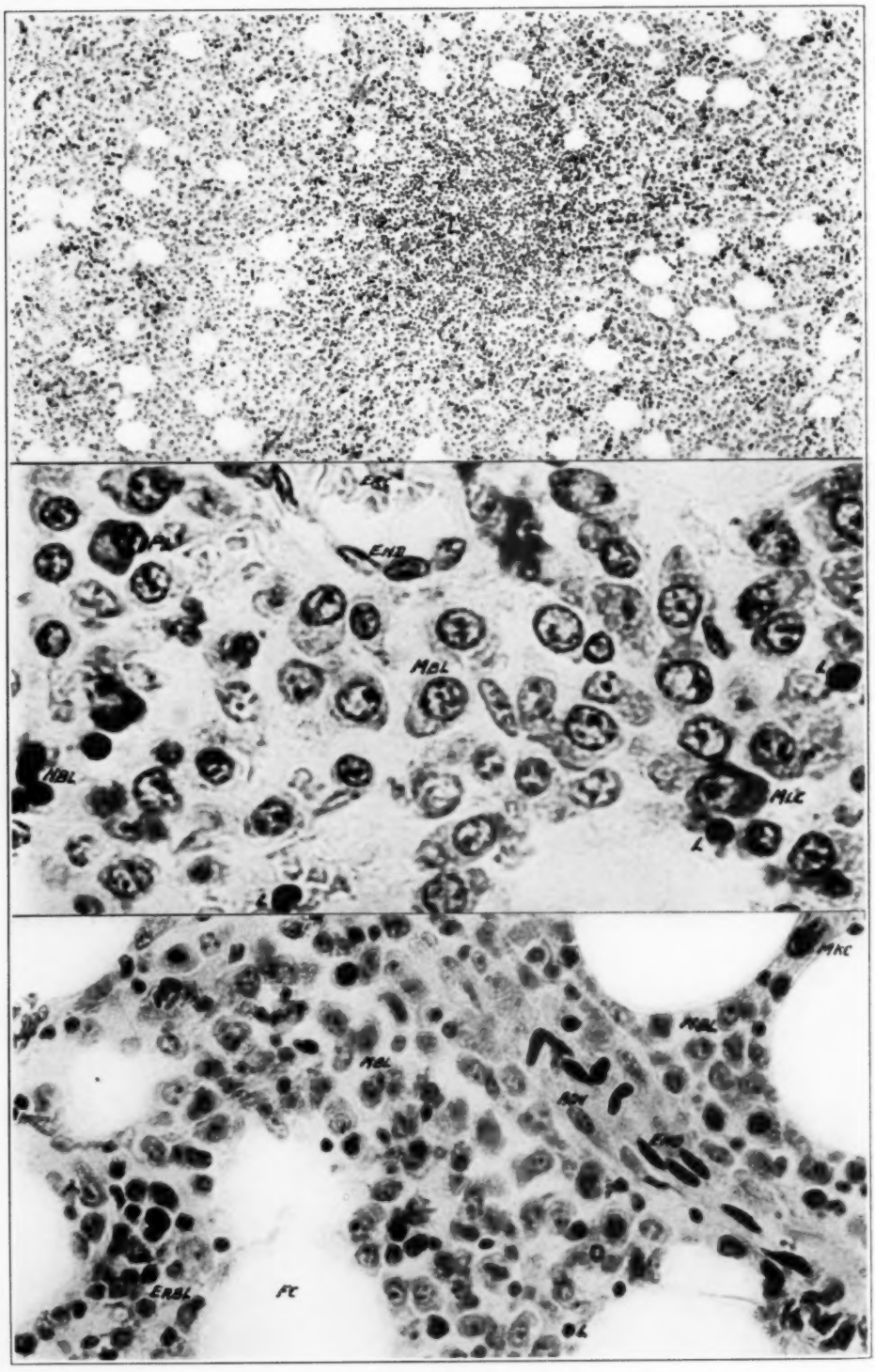

PLATE II.

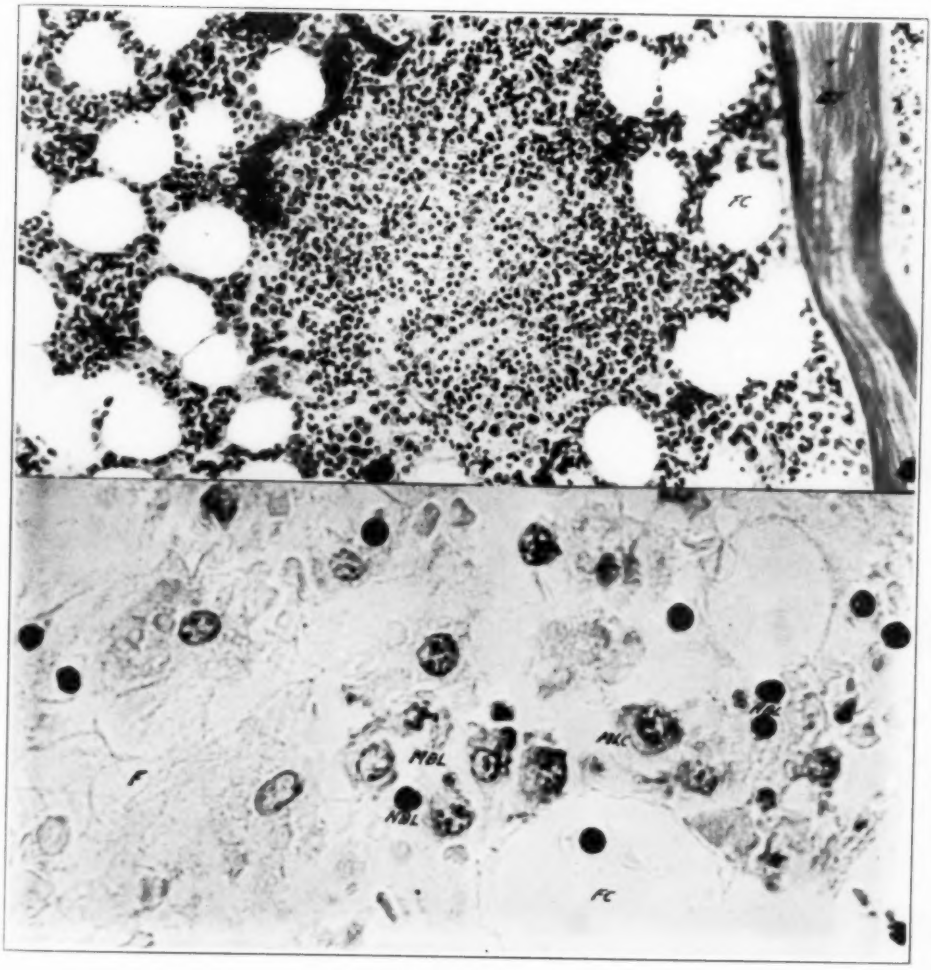

PLATE III.

Appearance of megakaryoblasts and megakaryocytes in increasing numbers with chronicity of the disease appears to keep pace with the myeloblastic hyperplasia. An infiltration of lymphocytes and plasmocytes is apparent from the first and becomes more and more prominent.

Discussion. My findings in the bone marrow are very similar to those carefully described by Jaffé[5] and include features mentioned by other observers, especially Oppikofer;[6] my interpretations are considerably different. The paramount feature is the failure of the actively proliferating myeloblasts to ripen into the segmented form of the neutrophil. Is this due to lack of an intrinsic maturation factor, as suggested heretofore by Fitz-Hugh and Krumbhaar,[7] and comparable to that of the erythron in pernicious anemia; or is it due to the influence of an extrinsic chemical or bacterial toxin? I believe the former to be true. I cannot agree with Jaffé that the marrow in arsenical and septic neutropenia does not differ from that in idiopathic agranulocytosis. The separation is difficult when one finds a relatively hypoplastic marrow, although still possible; comparison of the differential count from a typical regenerating marrow of each (Table 2) brings out a marked difference. Granular forms in the neutrophil series predominate in the arsenical and septic types and there is complete maturation never seen in idiopathic agranulocytosis; degenerative changes in the first two, when present, may affect all cell types, especially in the septic cases.

In agranulocytosis unquestionable degenerative changes in the cells of the granular series impressed me much more strongly while studying the first few cases of the series than they do now. In two of the group they are in the majority, in the others structurally good myeloid cells predominate. The first thought naturally is of a severe toxic degeneration which retards or inhibits maturation of the cells. But why specifically the granulocyte progenitors? It is obvious that myeloblasts cannot proliferate actively for days and months without some sort of disposal of their offspring; otherwise erythrocyte and thrombocyte groups would be crowded out as in the leukoses. It seems more logical to regard the degenerating forms as effete cells which succumb before reaching adolescence.

Causes of neutropenia have been schematically presented in the past. The following table, however, links the alteration in the blood with changes in the marrow in rough but practical fashion and affords the clinician better opportunity for classification of his cases as idiopathic or symptomatic agranulocytosis.

The term agranulocytosis has achieved such popularity that it will no doubt continually be applied to cases of marked neutropenia of obscure nature, whether other clinical features meet the diagnostic criteria of the idiopathic type described here or not. Fortunately, there is an increasing tendency to catalogue the atypical

cases as "secondary agranulocytosis" until the course of the disease or the pathologic findings permit proper etiologic classification (*e. g.*, arsphenamin neutropenia, etc.; compare Table 3). An analogue of the present situation may be recalled from the last century. Gretzel (1866) divorced from the leukemic leukoses, and designated as "splenic anemia" a large group of cases having common features, namely splenomegaly and anemia. Gradually the specific disease entities were withdrawn, so that, as Moynihan puts it, "the group is raided on every side. What remains? Only the forms of splenic anemia the cause of which is unknown." The raid on "agranulocytosis" is reaching such proportions that today it is the comparatively rare case that bears up under discriminating scrutiny in supporting the diagnosis of idiopathic agranulocytosis.

TABLE 3.—ABSENCE OR STRIKING DIMINUTION IN NUMBER OF NEUTROPHILS IN THE BLOOD STREAM.

I. With relatively **"full" marrow,** as result of:
  (*a*) Severe toxemia (usually bacterial), through primary stimulation of granulopoietic tissue, then destruction of cells *in situ* or on entry into the circulating blood.
  (*b*) The leukoses (leukemias), *viz.*:
    1. Aleukemic myelosis, through overproduction of granulocytes that either do not leave the marrow or are destroyed on entering blood.
    2. Lymphadenosis, through replacement of granulopoietic tissue.
    3. Reticulosis, through replacement of granulopoietic tissue.
  (*c*) Idiopathic agranulocytosis (agranulocytosis of Schultz, agranulocytic angina, malignant neutropenia), through defective maturation of myeloblasts (most cases show full marrow; see II-e).

II. With relatively **"empty" marrow,** as result of:
  (*a*) Severe toxemia (usually chemical), sometimes specific for neutrophils (benzol).
  (*b*) Marrow exhaustion, through protracted anemia, toxemia or infection.
  (*c*) Aplastic anemia (idiopathic), congenital or acquired.
  (*d*) Irradiation (Roentgen ray or radium).
  (*e*) Idiopathic agranulocytosis (the occasional case).

Summary. 1. Unwarranted diagnoses of agranulocytosis have appeared in the literature; lack of critical analysis of clinical and pathologic findings has confused the issue.

2. Meticulous study of the marrow from long and flat bones at necropsy is indicated in any case presenting marked neutropenia during life; sternal biopsy is suggested if the patient's condition permits.

3. Uniform findings in the bone marrow in 9 of 11 cases of proven idiopathic agranulocytosis are:

  (*a*) Marked proliferation of myeloblasts.
  (*b*) Failure of these cells to mature, resulting in paucity of myelocytes and practically complete absence of segmented forms.
  (*c*) Normal or slightly increased red blood cell formation.
  (*d*) Slight hyperplasia of otherwise normal megakaryocytes.
  (*e*) Infiltration of lymphocytes and plasmocytes.

4. Degeneration and relative hypoplasia are noted in 2 cases, although qualitative changes are similar to the other 9.

5. Comparison of differential marrow counts from idiopathic and secondary agranulocytosis (arsphenamin and septic neutropenia) shows marked dissimilarity.

6. Presence of a lesion of maturation specifically confined to the granulopoietic series, not reduplicated by diseases of known etiology, entitles idiopathic agranulocytosis, tentatively at least, to a place as a disease entity.

NOTE.—I am indebted to Dr. F. E. Ahlfeldt for assistance in a survey of the literature preliminary to this study and in collection of the material.

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A STUDY OF THE DIAGNOSTIC VALUE OF STERNAL PUNCTURE IN CLINICAL HEMATOLOGY.

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RECENT advances in our knowledge of the disorders of the blood have made clinicians increasingly conscious of the necessity for accurate hematologic diagnosis. Formerly a routine physical examination and blood count by an intern or the hospital laboratory was considered adequate in studying cases of anemia. Today in our larger hospitals the hematologist is called in consultation as freely as the surgeon or the nose and throat specialist, and it is important that he have at his command every possible diagnostic facility.

During the past year the author has employed sternal puncture routinely on all cases of blood dyscrasias seen in consultation. Needless to say the results have been extremely interesting.

The technique of sternal puncture has been described in detail elsewhere,[1] so that a brief résumé only will be given. A small

area on the skin overlying the sternum opposite the 3d interspace is painted with iodin, and novocain is injected into the skin, underlying tissues and periosteum. A specially constructed needle (Fig. 1) is then driven into the spongy bone and 10 cc. of bloody fluid aspirated and mixed with 2 cc. of a 1.4% sodium oxalate solution. This mixture is centrifuged and smears are made of the buffy coat and stained with Jenner-Giemsa stain. A differential count of 1000 cells is then made.

FIG. 1.—Needle used for sternal puncture

This method is practically painless and is well adapted to ward and clinic use. The small puncture heals up readily and the procedure can be repeated at frequent intervals.*

The marrow picture not only makes the diagnosis more definite, but presents a broadening insight into the changes going on in the formative tissues. A few selected cases will aid in illustrating the value of this technique. In describing the blood and bone marrow findings the following abbreviations will be used and percentage signs will be omitted:

Neutrophil polys. (mature forms)	Polys.
Neutrophil polys. (band forms)	Polys. B.F.
Neutrophil polys. (young forms)	Polys. Y.F.
Monocytes	Mon.
Lymphocytes	Lymph.
Eosinophils	Eos.
Basophils	Bas.
Myeloblasts	MBl.
Premyelocytes and myelocytes	MCY.
Normoblasts	NBl
Megaloblasts	MgBl.
Erythroblasts	EBl.
Proerythroblasts	PEBl.
Plasma cells	Pl.

Case Abstracts. CASE 1.—(Fig. 2.) Diagnosis: Normal; male, aged 32. Blood: Hb., 90; R.B.C., 5; W.B.C., 7300; Polys, 70; Lymph., 9; Mon., 11.

Marrow: Polys., 25; Polys. B.F., 10; Polys. Y.F., 5; Lymph., 10; Mon., 1; Eos., 1; MBl., 2; MCY, 20; NBl., 15; EBl., 8; PEBl., 2; Pl., 1.

CASE 2.—(Fig. 3.) Diagnosis: Secondary anemia.

The patient, a white female, aged 57, had been slowly losing weight and strength during the past 6 months. Owing to gastric distress she had restricted her diet for the past year to milk and white cereals. On exam-

* While the method of sternal puncture is undoubtedly of great value in the study of anemia, the examination of the material obtained in tissue sections rather than in smears would seem to be preferable. Imprint preparations break up fewer cells than do smears; with smears, preliminary suspension in serum has advantages.—EDITOR.

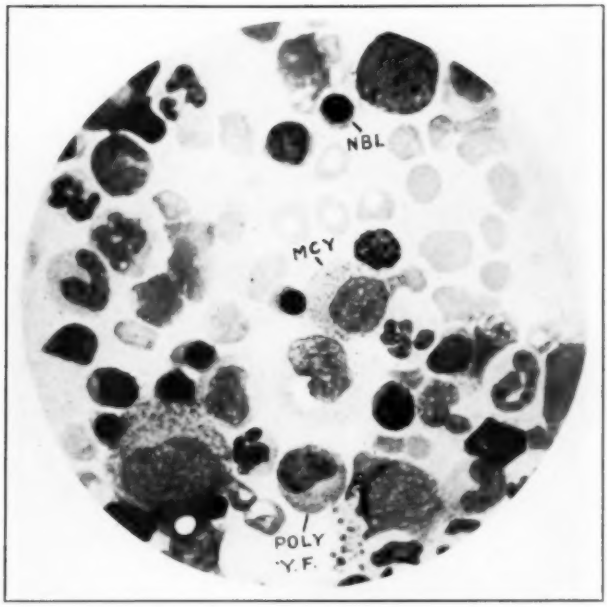

FIG. 2.—Sternal marrow. (666 ×.) Normal case.

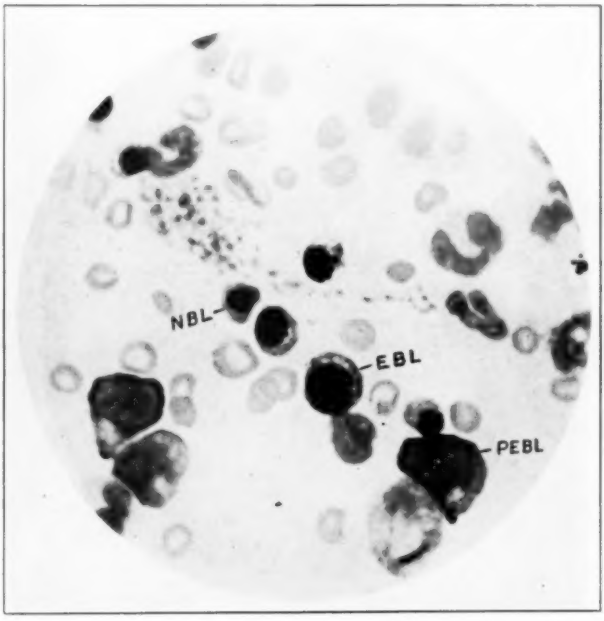

FIG. 3.—Sternal marrow. (666 ×.) Case of secondary anemia. Note normoblasts (*NBL*), erythroblasts (*EBL*) and pro-erythroblasts (*PEBL*).

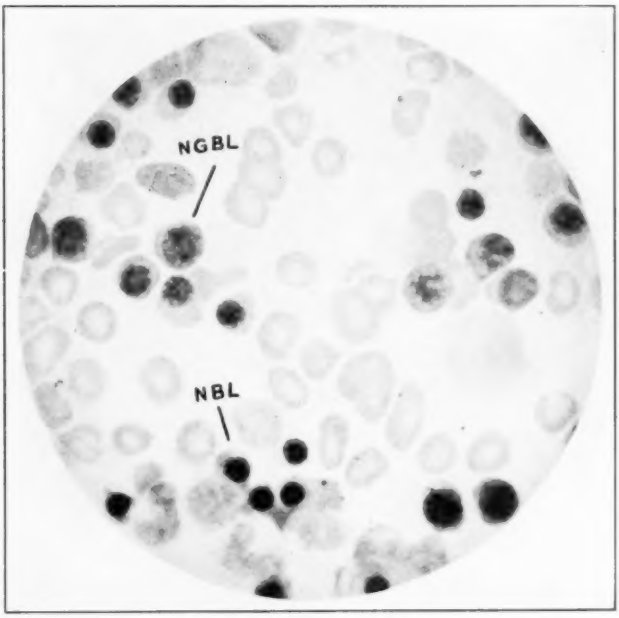

FIG. 4.—Sternal marrow. (666 ×.) Case of pernicious anemia. Note normoblasts (*NBL*) and megaloblasts (*NGBL*).

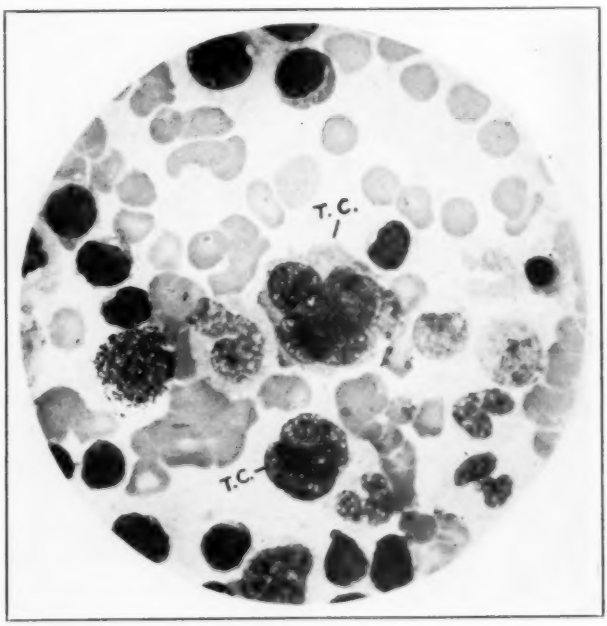

FIG. 5.—Sternal marrow. (666 ×.) Case of carcinoma of prostate with tumor cells in marrow. Note multinucleated tumor cells (*T.C.*).

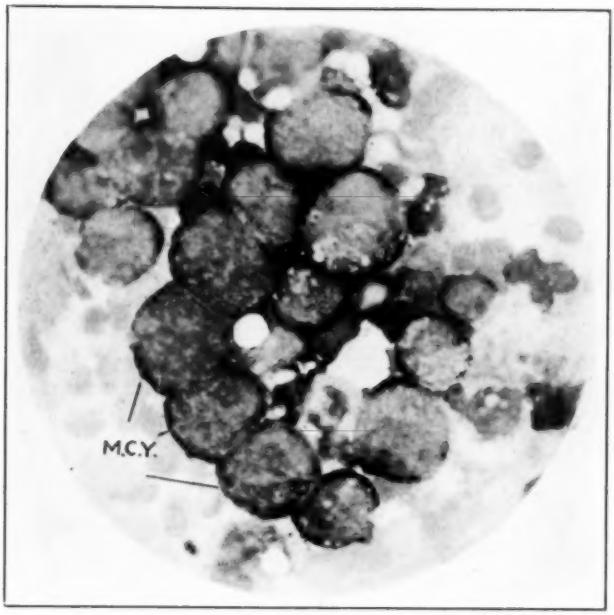

FIG. 6.—Sternal marrow. (666 ×.) Case of agranulocytosis with maturation arrest. Note presence of large numbers of myelocytes (*M.C.Y.*).

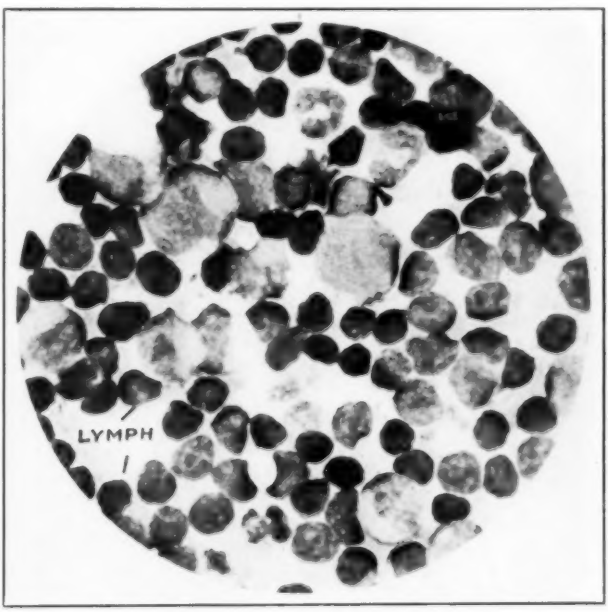

FIG. 7.—Sternal marrow. (666 ×.) Case of aleukemic lymphatic leukemia. Note extensive infiltration of marrow by lymphocytes (*lymph*).

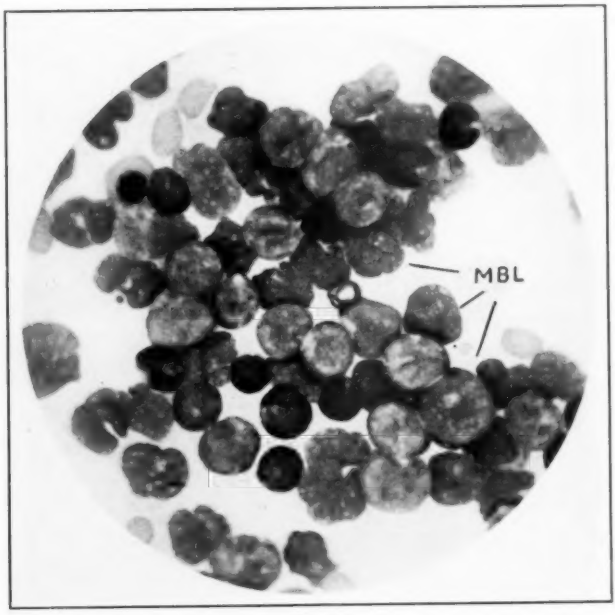

FIG. 8.—Sternal marrow (666 ×.) Case of acute myeloblastic leukemia. Note tremendous proliferation of myeloblasts (*MBL*), many of which have lobulated nuclei.

ination she was quite pale and showed swollen and bleeding gums similar to those seen in scurvy.

Blood: Hb., 53; R.B.C., 2.8; W.B.C., 5000; Polys., 68; Lymph., 24; Mon., 6; Eos., 1; Bas., 1.

Marrow: Polys., 17; Polys. B.F., 13; Polys. Y.F., 5; Lymph., 5; MBl., 3; MCY., 13; NBl., 25; EBl., 15; PEBl., 3; Pl., 3.

She was put on a high-vitamin diet with particular attention to fresh fruits. Iron by mouth in large doses was also given. Recovery took place with startling rapidity.

This is a case of secondary anemia caused by dietary deficiency. It is very similar to the nutritional anemia of infancy. The bone marrow showed the typical normoblastic and erythroblastic activity seen in secondary anemia.

Case 3.—(Fig. 4.) Diagnosis: Pernicious anemia.

The case was that of a white male, aged 46. He had a typical history of slowly increasing weakness and pallor. His tongue was atrophic and he suffered from paresthesia in the lower extremities with loss of vibratory sense over the tibia. The liver and spleen were enlarged, and the stomach contents showed no free HCl after histamin stimulation. The blood Wassermann test was negative and a gastro-intestinal barium study showed no lesions.

Blood: Hb., 68; R.B.C., 2.9; W.B.C., 5800; Polys., 58; Lymph., 24; Mon., 10; Eos., 8.

Marrow: Polys., 2; Polys. B.F., 3; Polys. Y.F., 3; Lymph., 2; MBl., 2; MCY., 3; NBl., 62; MgBl., 12; EBl., 10; PEBl., 1.

The marrow showed marked erythroblastic activity with the presence of numerous megaloblasts, which is characteristic of pernicious anemia. Treatment with liver extract produced the expected good results.

Case 4.—Diagnosis: Carcinoma of prostate with pernicious anemia blood picture.

A man, aged 31, had increasing weakness and pallor extending over a period of several months. A diagnosis of pernicious anemia had been made elsewhere and liver treatment used to no avail. He was admitted to the hospital acutely ill, with a temperature of 105° F.

Blood: Hb., 51; R.B.C., 2; W.B.C., 1500; Polys., 20; Lymph., 70; Mon., 10.

A tentative diagnosis of agranulocytosis was made.

Marrow: Polys., 9; Polys. B.F., 1; Lymph., 3; MBl., 1; MCY., 14; NBl., 22; MgBl., 20; EBl., 26; PEBl., 3; Pl., 1.

Marked erythroblastic activity of the pernicious anemia type was seen in the marrow. The patient expired and at autopsy was found to have a carcinoma of the prostate with metastases.

This case illustrates the fact that carcinoma can often produce a blood and bone marrow picture similar to that seen in pernicious anemia.

Case 5.—(Fig. 5.) Diagnosis: Carcinoma of the prostate. (Showing tumor cells in the marrow.)

The history of this white male, aged 60, was one of increasing weakness and ill-health. Physical examination was negative except for evidence of anemia and loss of weight. A gastro-intestinal barium study was negative as was also the blood Wassermann test.

Blood: Hb., 82; R.B.C., 4; W.B.C., 22,000; Polys., 30; Lymph., 52; Lymphoblasts, 3; Mon., 11; Eos., 3; Bas., 1.

The possibility of lymphatic leukemia was suggested.

Marrow: Polys., 22; Polys. B.F., 6; Lymph., 2; Eos., 1; MCY., 9; NBl., 4; EBl., 2; Tumor cells, 54.

Many of the tumor cells were multinucleated and did not resemble any known marrow cell.

Roentgen ray of the bones showed the mottling peculiar to carcinoma. Autopsy revealed a carcinoma of the prostate with metastases.

The presence of tumor cells in the sternum is unusual, but the sternal puncture not only ruled out leukemia in this case, but made the diagnosis of carcinoma as well.

CASE 6.—(Fig. 6.) Diagnosis: Agranulocytosis. (With maturation arrest. Recovery.)

The patient was a white female, aged 55, who had been in good health up to 1 week before admission to the hospital, when she began to get sores in the mouth and felt sick. Her temperature was 103° F. and she was quite ill.

Blood: Hb., 85; R.B.C., 4.8; W.B.C., 1100; Polys., 5; Lymph., 80; Mon., 15.

Marrow: Polys., 0; Polys. B.F., 1; Lymph., 8; MBl., 3; MCY., 70; NBl., 9; EBl., 8; PEBl., 1.

The diagnosis of agranulocytosis with maturation arrest was made and she was treated with transfusions and injections of aolan. Within a few days the temperature came down and she got well. Since that time she has been observed for a period of months and has been found to have a state of chronic agranulocytosis.

CASE 7.—Diagnosis: Agranulocytosis. (With maturation arrest. Fatal outcome.)

The case was that of a young woman, aged 20, suffering from chronic pulmonary tuberculosis. For the past few months she had taken large doses of barbiturates for insomnia. Three weeks before her demise her temperature began to mount and she had small ulcers in the mouth.

Blood: Hb., 60; R.B.C., 3.5; W.B.C., 1300; Polys., 18; Lymph., 82.

Marrow: Polys., 5; Lymph., 12; MBl., 18; MCY., 53; NBl., 10; EBl., 2.

The diagnosis of agranulocytosis with maturation arrest was made. The usual treatment was instituted, but she did not respond and expired.

CASE 8.—Diagnosis: Agranulocytosis. (With marrow aplasia. Fatal outcome.)

The patient was a white male, aged 55, who had been in the hospital for 2 months, suffering from a poorly healing fracture of the left hip. Ten days before his death he began to feel vagulely ill and his temperature rose to 103° F. The abdomen was distended and tender and at times he was irrational.

Blood: Hb., 53; R.B.C., 2.5; W.B.C., 1500; Lymph., 80; Mon., 20.

The sternal puncture yielded a markedly diminished quantity of bone marrow. The count was:

Marrow: Lymph., 70; Mon., 10; MCY., 1; EBl., 4; Pl., 9; PEBl., 6.

A diagnosis of agranulocytosis with marrow aplasia was made.

The patient did not respond to any therapy but ran a continued high temperature and died 10 days after the onset of this acute illness.

Autopsy: Bronchopneumonia, acute pericarditis, acute splenitis and marked ulcerations of the small and large intestine.

It was interesting to note that on microscopic examination no polys. could be found in the pneumonic areas in the lung.

The last 3 cases of agranulocytosis illustrate very well the underlying pathologic changes so well described by Fitz-Hugh and Krumbhaar.[2] A large number of these cases show a hyperplasia of the myeloid elements rather than an aplasia, and strengthens the suggestion that in many instances the condition is secondary to a maturation arrest.

CASE 9.—(Fig. 7.) Diagnosis: Aleukemic lymphatic leukemia.

The patient was a white male, aged 55. He had large masses of glands in the neck, axilla and groin, along with enlargement of the spleen.

Blood: Hb., 80; R.B.C., 4.1; W.B.C., 6000; Polys., 53; Lymph., 32; Mon., 10; Eos., 5.

Marrow: Polys., 3; Polys. B.F., 3; MCY., 4; NBl., 3; Lymph., 87.

The marrow showed a marked infiltration with lymphocytes and a diagnosis of aleukemic lymphatic leukemia was made. Biopsy of a lymph node confirmed this diagnosis.

CASE 10.—Diagnosis: Lymphoma.

For the past few years, the patient, a male, aged 70, had noticed swelling of the glands in his neck, axilla and groin. These glands were markedly enlarged, as were also the spleen and liver. He came into the hospital suffering from dyspnea and was found to have a left hydrothorax. The temperature was normal. Chest tap yielded 1500 cc. of chylous fluid, with improvement in his symptoms.

Blood: Hb., 105; R.B.C., 5.5; W.B.C., 10,200; Polys., 50; Polys. B.F. 10; Lymph., 37; Mon., 1; Eos., 2.

There was some talk of lymphatic leukemia, but the lack of anemia seemed to be against this.

Marrow: Polys., 52; Polys. B.F., 12; Polys. Y.F., 3; Lymph., 16; Bas., 1; Eos., 10; MCY., 5; NBl., 1.

The lack of lymphocytic infiltration in the marrow was definitely against leukemia. *Biopsy* of a lymph node was diagnosed as lymphoma, with no evidence of leukemia.

CASE 11.—(Fig. 8.) Diagnosis: Acute myeloblastic leukemia.

The case was that of a male, aged 23. He had always been well up to 1 month before admission to the hospital. At this time he began to complain of weakness and shortness of breath. On admission to the hospital he was acutely ill. His temperature was 102° F., the spleen was slightly enlarged and there were hemorrhages in the eyegrounds.

Blood: Hb., 35; R.B.C., 2.2; W.B.C., 150,000; Polys., 5; Lymph., 11; MCY., 3; MBl., 81.

There was some doubt in the mind of one of the clinicians as to whether these cells were myeloblasts or lymphoblasts.

Marrow: MBl., 92; NBl., 8.

The diagnosis of acute myeloblastic leukemia was, therefore, definitely established.

Summary. From a study of the cases cited, it is seen how valuable sternal puncture may be in differentiating the various types of anemia, in establishing the diagnosis of leukemia in doubtful cases and in differentiating aleukemic lymphatic leukemia from agranulocytosis. In 1 instance it was even possible to see tumor cells in the sternal marrow, although this is very unusual.

This method of investigation does much more for the hematologist, however, than aid him in his diagnosis. It gives him an insight into the fundamental processes underlying his findings in the peripheral blood and opens new avenues of clinical research. It is now possible to study the changes in the bone marrow almost as frequently as those in the peripheral blood and to observe the direct effect of therapy on the formative tissue.

Conclusions. 1. A technique of sternal puncture was described which can be done repeatedly with a minimum of discomfort to the patient.

2. A series of cases were reported which show that study of the bone marrow obtained in this way is of great assistance in hematologic diagnosis.

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THE EFFECT OF ULTRAVIOLET RAYS ON SNAKE VENOMS.*

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In recent years the subject of snake venoms has been of interest not only from the standpoint of toxicology but also to some extent from that of experimental therapeutics. As far back as 1910 and 1914, papers were published by Mays,[1] Fackenheim,[2] Prévost,[3] Jenkins and Pendleton,[4] Thom[5] and others on the uses of crotalin, or the poison of rattlesnake, in the treatment of epilepsy; and within the last year or two, French investigators have reported studies concerning the use of cobra venom in the treatment of inoperable malignant tumors.[6,7,8,9,10] The present investigation was undertaken for the purpose of advancing our knowledge concerning the various factors and conditions influencing the activity of snake venoms and concerning methods of standardizing and preserving them for experimental work.

It is common knowledge that many drugs and chemicals are affected by physical agents, particularly by heat and light. It is also well known that suspensions or solutions of snake venoms decompose on standing and deteriorate under the influence of temperature. The venoms of the Crotalidæ are especially labile and easily affected in this respect. The venoms of the Elapidæ, and particularly that of Naia or cobra, are more resistant to heat. With regard to the effect of light on snake venoms, Calmette[11] noted that solutions of these toxins deteriorate when exposed to sunlight. Noguchi[12] studied the photodynamic effect of eosin and erythrosin on snake venoms and found that in sunlight these dyes decrease the toxicity of the venoms. Massol[13] found that the rays of the quartz lamp decomposed cobra venom; and Phisalix[14] noted

* Read before the Optical Society of America, at its Nineteenth Annual Meeting, Friday, October 19, 1934, in Washington, D. C.

that very long exposure (for 60 hours) of this toxin to radium radiations reduced its activity. The present investigation is devoted to a more detailed study of different ultraviolet radiations on a number of snake venoms.

Method. Studies were made chiefly on the venoms of two great classes of snakes, namely, of the Elapidæ, the principal representative of which is the cobra; and on the poisons of the viper group, the Crotalidæ, the American representative of which is the rattlesnake. In all experiments performed, the dried scales of venom were dissolved or brought into a colloidal solution either in water or, more often, in physiologic saline. The cobra venom employed in this investigation was obtained through the courtesy of Prof. R. N. Chopra, of the School of Tropical Medicine, Calcutta, while the Crotalus venom, or the poison of the rattlesnake, was procured through the kindness of the Mulford Biological Laboratories, Philadelphia. Venom was obtained from different species of rattlesnake, namely, the Crotalus atrox, Crotalus ruber and Crotalus exsul. In addition, other experiments were made with the venoms of Ancistrodon, or copperhead, and Bothrops atrox, South American viper.

In accordance with the character of experiment to be performed, the dried scales of venom were rubbed up carefully in glass mortars with either distilled water or saline solution. As will be seen later, venom suspensions prepared from different samples of snake poisons varied greatly in their potency. Whenever a pharmacologic experiment was performed, therefore, great care was taken to make suitable control tests in order to establish the toxicity of the solution used on each particular day.

Method of Irradiation. Ultraviolet radiations were obtained from mercury vapor quartz lamps. The particular apparatuses used were the Alpine Sun lamp and the Kromayer lamp of the Hanovia Manufacturing Company. Since the Alpine Sun lamp emits and generates a great deal of heat, which must be taken into account in studying the effect of ultraviolet rays on chemicals and drugs, most of the experiments were made with the the water-cooled Kromayer lamp. When this apparatus is used, temperature need not be considered. The quality and quantity of radiations emitted by the Kromayer lamp are shown in the subjoined graph, prepared by Dr. W. T. Anderson, Jr. This chart indicates the distribution of spectral energy of the burner employed in the experiments at a distance of 4 inches from the window of the Kromayer lamp. When the present investigation was in progress, the intensity of radiation was considerably greater because snake venom solutions in small quartz tubes were placed directly against the window of the Kromayer lamp. In addition to such radiations as are indicated in Fig. 1, the Alpine Sun lamp emits waves as low as 1800 Ångström units which are absorbed by the water of the Kromayer lamp, and also some longer waves.

Studies on the effect of such ultraviolet irradiation on snake venoms were made not only with the total energy emitted by the Kromayer lamp but also with longer and shorter ultraviolet rays emitted by the lamp, respectively, when various filters were used. Specifically, some experiments were made with rays passed through a Wood filter, which cuts out all but the very long ultraviolet rays, while others were performed with rays passed from a Kromayer lamp through a clear quartz cylinder containing chlorin gas, which absorbs the wave lengths between the regions of 3000 and 4050 Ångström units and allows only the shorter ultraviolet rays to be transmitted.

Through the courtesy of Dr. C. F. Burnam, of the Howard A. Kelly Hospital, Baltimore, the writer was also enabled to study the effects of hard Roentgen rays and radium radiations on snake venoms.

Pharmacologic Methods of Study. The toxicity or potency of the venoms was assayed or tested on mice, rats, guinea pigs, rabbits and cats. In this connection, mice were found to be the most useful and economical test objects; and nearly 300 experiments were performed on these animals, the average weight of which was about 20 gm. Injections in both mice and rats were made by the subcutaneous, intramuscular and intraperitoneal routes. No marked difference in the onset of toxic symptoms was noted after parenteral and intraperitoneal injections, respectively. In order to make a more detailed analysis of their pharmacologic action on the circula-

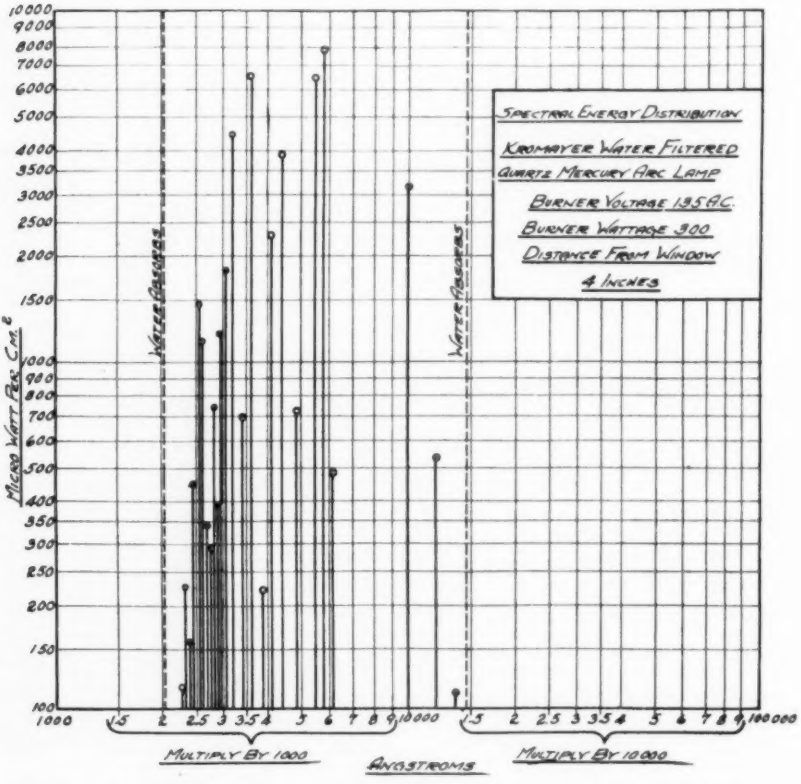

FIG. 1.—Distribution of spectral energy of burner employed in experiments.

tion and respiration, very dilute solutions of venom were injected intravenously at regular intervals in cats kept under light ether anesthesia. Such injections were made through the femoral vein while blood pressure tracings were recorded from a cannula inserted into a carotid artery; and respiratory tracings were obtained directly through the trachea by a method which the author has described elsewhere.[15] Beside the zoöpharmacologic studies mentioned above, parallel experiments were made on phytopharmacologic test objects, namely, on the living seedlings of Lupinus albus, which have been found to be susceptible to snake venom solutions.[16]

The entire investigation was divided into two distinct parts. One series of experiments was devoted to the study of the effects of ultraviolet radiations on various suspensions of snake venoms in quartz cells or containers. Another series of experiments was performed for the purpose of discovering the effect of ultraviolet irradiation on animals *previously* injected with varying doses of snake venoms. The object of these experiments was to ascertain whether any antidotal or antagonistic, and hence therapeutic, effect could be secured by such irradiation. A detailed description of the results obtained follows:

Irradiation of Venom Solutions. *Effect of Total Radiation.* Colloidal suspensions of rattlesnake and cobra venoms were made in physiologic saline, placed in rectangular quartz cells, and irradiated in the manner described above for varying periods. It was found that even a short exposure (*i. e.*, for 5 minutes) of the solutions to the rays emitted by the Kromayer lamp produced rapid deterioration of their toxicity, as indicated by biological tests on both plants and animals. In this respect it was noted that cobra venom was somewhat more resistant to ultraviolet rays than rattlesnake venom, but all the other snake venoms proved to be sensitive to the radiations of the mercury vapor lamp. Exposure for 5 minutes produced a noticeable decrease in toxicity, while a 10-minute exposure to the Kromayer lamp effected a marked deterioration of the venom solutions. The results obtained in various experiments are well illustrated by Tables 1 and 2.

TABLE 1.—EFFECT OF PROGRESSIVE IRRADIATION OF COBRA VENOM WITH KROMAYER LAMP.

In Experiments on Mice.	*In Experiments on Lupinus Albus.*
1. Injected 0.1 mg. of cobra venom, unirradiated. Dead in 1 hour and 35 minutes.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, unirradiated, 53%.
2. Injected 0.1 mg. of cobra venom, irradiated 10 minutes. Dead in 15 hours.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, irradiated 10 minutes, 68%.
3. Injected 0.1 mg. of cobra venom, irradiated 20 minutes. Made sick but recovered.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, irradiated 20 minutes, 79%.
4. Injected 0.1 mg. of cobra venom, irradiated 30 minutes. Very little toxicity exhibited.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, irradiated 30 minutes, 85%.

Table 1 shows the effect of progressive irradiation of solutions of cobra venom when quartz cells containing them were placed against the window of the Kromayer lamp. Experiments on both mice and seedings of Lupinus albus revealed a striking, progressive deterioration of the cobra venom thus irradiated. Whereas the normal killing time of the solution for mice was 1 hour and 35 minutes,

the killing time of the same solutions after irradiation for 10 minutes was 15 hours. More prolonged irradiation rendered the solutions no longer fatal. Similarly the phytotoxic index of Lupinus albus seedlings grown in a solution of 1 to 100,000, which was originally 53%, rapidly rose to a higher figure with progressive irradiation of the venom. Table 2 shows the effect of venoms of the rattlesnake (Crotalus exsul), the South American viper (Bothrops atrox), the copperhead (Ancistrodon piscivorus) and of the cobra (Naia tripudians) on the growth of Lupinus albus seedlings. Phytopharmacologic tests were especially useful in comparative studies performed simultaneously on various solutions. The table shows the average root growth at a temperature of 21° C., for 24 hours, of 50 seedlings in solutions of snake venoms as compared with growth of control seedlings in normal plant-physiologic solution. The toxicity of the venoms both before irradiation and after exposure to the Kromayer lamp for 15 minutes is here recorded. In these studies the writer employed a concentration of cobra venom higher than that used in the experiments recorded in Table 1.

TABLE 2.—EFFECT OF VENOMS ON GROWTH OF LUPINUS ALBUS.

Venom.	Concentration.	Phytotoxic index of seedlings grown in	
		Fresh emulsion, %.	Emulsion exposed to Kromayer lamp for 15 min., %.
Crotalus exsul	1 to 10,000	36	77
Bothrops atrox	1 to 10,000	55	100
Ancistrodon piscivorus	1 to 10,000	44	100
Naia tripudians (cobra)	1 to 10,000	32	88

Effect of Long Rays. In order to ascertain accurately the effectiveness of different ultraviolet rays in the detoxification of the venoms, experiments were made in which rays from the Kromayer lamp were passed through various filters excluding certain wave lengths and transmitting others. In this investigation, the two filters used were the Wood filter and a chlorin gas filter. The Wood filter, made of nickel oxid glass, cuts out all short waves emitted by the mercury lamp and transmits only the wave lengths over 3000 Ångström units. Solutions of venoms were exposed to rays transmitted through such a filter, and it was found that even after very long exposures (of 1 hour or more) little or no change had been produced in the potency of the venoms. The following protocol will illustrate the findings obtained in such experiments:

Experiment of May 22, 1934.

1. Five control mice were each injected with 0.1 mg. of cobra venom in solution, which had not been irradiated. Average killing time, 1 hour and 25 minutes.
2. Three mice were each injected with 0.1 mg. of the same solution, previously irradiated for 1 hour by rays passing through Wood filter. Average killing time, 1 hour and 30 minutes.

Effect of Short Waves. The effect of the short ultraviolet rays emitted by the Kromayer lamp was studied as follows: A clear quartz cylinder containing chlorin gas was interposed between the Kromayer lamp and the venom solutions. Such a filter cuts out all the ultraviolet rays ranging from 3000 to 4000 Ångström units but transmits those of shorter wave length. The following protocols indicate clearly that exposure to such short waves for 1 hour produced but little decrease in toxicity of the venoms.

Experiment of May 23, 1934.

(With Rays Transmitted Through a Chlorin Gas Filter.)

1. Four mice were each injected with 0.1 mg. of cobra venom solution, which had not been irradiated. Average killing time, 1 hour and 26 minutes.
2. Four mice were each injected with 0.05 mg. of cobra venom solution, which had not been irradiated. Average killing time, 6 hours.
3. Four mice were each injected with 0.1 mg. of cobra venom solution, which had been irradiated for 30 minutes. Average killing time, 1 hour and 30 minutes.
4. Two mice were each injected with 0.1 cobra venom suspension which had been irradiated for 1 hour and 15 minutes. Average killing time, 20 hours.
5. Two mice were each injected with 0.05 mg. of cobra venom, which had been irradiated for 1 hour and 15 minutes. Both recovered.

Irradiation of Poisoned Animals.—The destructive action of ultraviolet rays on snake venom solutions in quartz containers having been established, the next step was to inquire whether such rays are capable of destroying or at least of decreasing the virulence of the venoms after they have been injected in animals. Accordingly, experiments were made on mice to which the venoms were administered in various ways; and, after injection, the animals were exposed to the rays of either the Kromayer lamp or the Alpine Sun lamp. In some experiments, such injections were made subcutaneously; in others, intramuscularly; and in still others, intraperitoneally. The animals in small cages were exposed to the rays of the Kromayer lamp at a distance of 20 cc. from the window. When the Alpine Sun lamp was employed for irradiation, the usual distance of the cage containing the animals from the mercury arc was about 60 cm. It may be stated at once that control experiments on normal mice, which had *not* been injected with snake venom revealed that such irradiation for protracted periods of time (*i. e.*, ½ hour or more) had no deleterious effect on these animals.

It was surprising to discover that the findings obtained in tests on animals were not at all in agreement with those obtained in experiments in which the venom had been placed in quartz containers and exposed to ultraviolet radiations. Animals injected with snake venom and then placed under mercury vapor lamps exhibited no diminution of toxic symptoms. Instead of exerting an antagonistic or detoxifying action, the irradiation of the injected

mice produced either no difference in the killing time of the animals or, as was more often the case, somewhat accelerated the onset of death. This was particularly true of cobra venom injections. Similar observations were made with Crotalus venom occasionally; when injections of solutions of this venom were made in the skin of the back—that is, in a site from which the poison was not readily absorbed—a decrease in the toxicity or delay in the onset of toxic symptoms was noted. Such an effect, however, was never observed after injection of cobra venom by any route.

TABLE 3.—EFFECT OF IRRADIATION BY ALPINE SUN LAMP ON MICE AFTER INJECTION OF CROTALUS ATROX VENOM.

Mouse No.	Injected.	Irradiated.	Effect.
1	Not injected	30 min.	None.
2	0.5 mg., subcut.	Unirradiated	Dead in 1 hr., 45 min.
3	0.5 mg., intraperit.	Unirradiated	Dead in 1 hr., 50 min.
4	0.5 mg., intraperit.	30 min.	Dead in 1 hr., 24 min.
5	0.5 mg., intramus.	30 min.	Dead in 1 hr., 35 min.
6	0.5 mg., subcut.	30 min.	Dead in 1 hr., 7 min.
7	0.5 mg., intraderm. in back	30 min.	Dead in 5 hr.

TABLE 4.—EFFECT OF IRRADIATION WITH KROMAYER LAMP ON MICE INJECTED WITH COBRA VENOM.

Mouse No.	Administered, % of mg.	Injected.	After injection.	Dead in.
1	0.250	Subcutaneously	Irradiated	17 min.
2	0.250	Subcutaneously	Unirradiated	16 min.
3	0.200	Intraperitoneally	Irradiated	25 min.
4	0.200	Intraperitoneally	Unirradiated	31 min.
5	0.100	Subcutaneously	Irradiated	2 hr., 12 min
6	0.100	Subcutaneously	Unirradiated	2 hr., 37 min.
7	0.100	Intraperitoneally	Irradiated	1 hr., 38 min.
8	0.100	Intraperitoneally	Unirradiated	2 hr.
9	0.050	Intraperitoneally	Irradiated	2 hr., 19 min.
10	0.050	Intraperitoneally	Unirradiated	2 hr., 39 min.
11	0.050	Intramuscularly	Irradiated	2 hr., 19 min.
12	0.050	Intramuscularly	Unirradiated	2 hr., 39 min.
13	0.025	Subcutaneously	Irradiated	5½ hr.
14	0.025	Subcutaneously	Unirradiated	Died overnight
15	0.020	Intraperitoneally	Irradiated	Recovered.
16	0.020	Intraperitoneally	Unirradiated	Recovered.

The results obtained are well illustrated in the subjoined Tables 3 and 4. Table 3 shows the effect of irradiation with the Alpine Sun lamp on 6 mice, previously injected with rattlesnake (Crotalus atrox) venom. The first or control mouse, which was not injected with snake venom at all, was exposed to ultraviolet rays and exhibited no toxic symptoms. The table shows the killing time of mice injected with the venom, some of which were irradiated while others were not. No marked difference in the killing time of the two sets of mice was noted; only in case of mouse No. 7, which had been injected intradermally in the back and exposed to ultraviolet

rays was the onset of death delayed. Table 4 shows the effect produced by injections of various doses of cobra venom in pairs of mice, 1 of which was exposed to ultraviolet radiations while the other was not. Here again, it will be noted that very little detoxification resulted from exposure of injected mice to ultraviolet rays.

Since detoxification did occur occasionally when the venom solution was injected in locations from which absorption was poor, additional experiments were made with solutions of venom combined with drugs, tending to prevent absorption. Such experiments were made with small doses of epinephrin, in some animals, and of solutions of sodium sulphate in others; and it was found that neither of these promoted detoxification of the venoms by ultraviolet rays.

Analysis of Results. The great difference between the effects of ultraviolet rays on snake venoms in quartz cells outside the body and their action on these toxins *in vivo* calls for an explanation. Various hypotheses may be advanced. It may be assumed that after injection the venom rapidly combines with body tissues and is no longer present in a form easily disintegrated by ultraviolet rays. Such an hypothesis does not tally with the fact that the poisonous action of cobra and other snake venoms for mice is not very rapid and that the minimal lethal dose for these animals usually produces death in an hour or more. Again, it may be argued that the ultraviolet rays do not destroy the venom injected in those animals because they do not sufficiently penetrate the skin and tissues of the animals. This view is not tenable, considering the fact that ultraviolet irradiations have been proven to be of undoubted efficacy in the treatment of rickets and other clinical diseases. Moreover, Macht, Anderson and Bell have shown that the penetration of ultraviolet rays, especially those with wave lengths between 3000 and 4000 Ångström units, through living tissue is much greater than was formerly supposed.[17,18] A third explanation for the difference between the effects of the rays on venoms in quartz cells and their action on the same toxins *in vivo* was obtained by actual experiment.

Solutions of cobra venom were prepared and divided into two portions. One-half was placed alone in a quartz cell. To the other half of the solution a small quantity of clear blood serum was added, and the mixture was placed in another quartz cell of the same proportions. The 2 specimens were irradiated simultaneously with the same lamp for the same length of time. The toxicity of each was then tested on mice and other animals. It was found that exposure of the plain venom solution in physiologic saline to the ultraviolet rays resulted in a marked decrease in its toxicity. On the other hand, exposure to ultraviolet rays of the snake venom solution, to which 5% or more of blood serum had been added,

produced very little change in its toxicity. The results obtained are concretely illustrated by the following protocols:

Experiment of October 9, 1934.

Mouse No. 1 (Control).

10.20 A.M.: Injected with 0.5 cc. of cobra venom solution (1 mouse unit).

2.10 P.M.: Dead.

Mouse No. 2.

10.21 A.M.: Injected with 2 cc. of cobra venom solution (4 mouse units), which had been irradiated with Kromayer lamp for 38 minutes, + 0.5 cc. of unirradiated cat serum.

5.30 P.M.: Very slight depression. Recovered next day.

Mouse No. 3.

10.22 A.M.: Injected with 2 cc. of cobra venom solution (4 mouse units) + 0.5 cc. of cat serum after the mixture had been irradiated for 38 minutes.

3.00 P.M.: Dead.

It is evident that blood serum exerts a protective action for snake venom against the destructive effect of ultraviolet radiations. Similar experiments were performed with various proportions of serum both from cats and from human beings with identical results.

Another striking illustration of the protective action of blood serum was obtained by biochemical experiments of an entirely different character. The oxidation reaction of fresh rat muscle was studied by Thunberg's method,[19] which need not be described in detail here. Briefly, it consists of observing the time required for the decolorization of a standard solution of methylene blue in specially constructed tubes from which all air has been exhausted. In such experiments 3 tubes were employed. In 1 tube was placed a solution of methylene blue to which a definite quantity of ground rat muscle and a small amount of physiologic saline solution were added, and the time required for decolorization of methylene blue at 37° C. was observed. This was the control experiment. In a second tube, a similar solution of methylene blue with ground muscle tissue and cat serum was placed; and 5 mg. of cobra venom, previously irradiated with a Kromayer lamp, were also added. In the third tube, an equal amount of cobra venom was introduced in a solution similar to that mentioned above, but in this case the venom used had been previously irradiated *together with* a similar quantity of blood serum. The venom irradiated alone became markedly detoxified, as indicated by the rapid decolorization of the methylene blue. On the other hand, the venom which had been irradiated together with the blood serum underwent little change and inhibited the action of the muscle oxidosis, so that no decolorization occurred. Such an experiment is illustrated by the following protocols.

A more graphic demonstration of this difference produced by irradiation of cobra venom with and without blood serum is afforded by the subjoined figures. These are kymographic tracings, showing

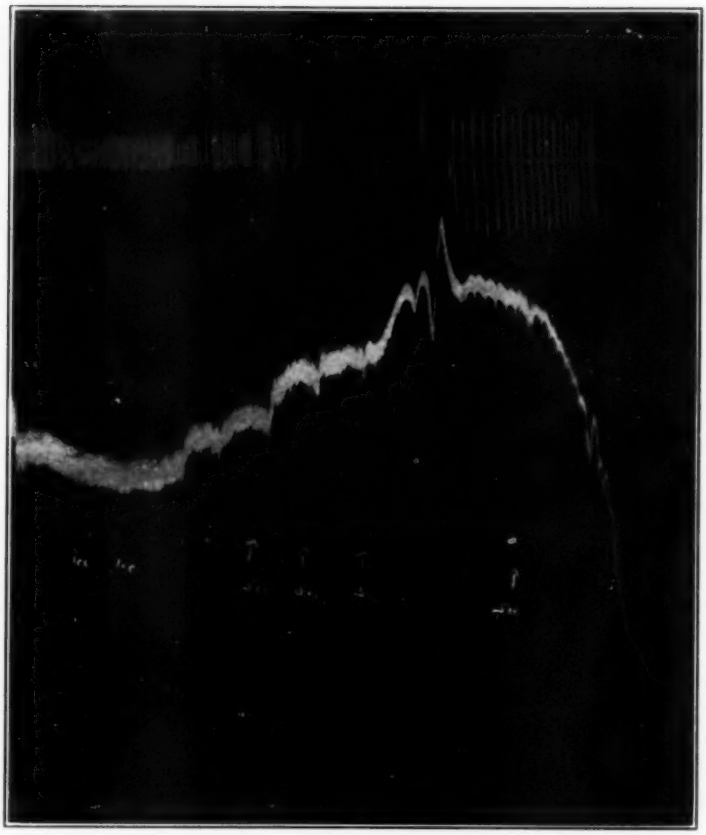

FIG. 2.—Showing effect of intravenous injection in cat of unirradiated cobra venom.

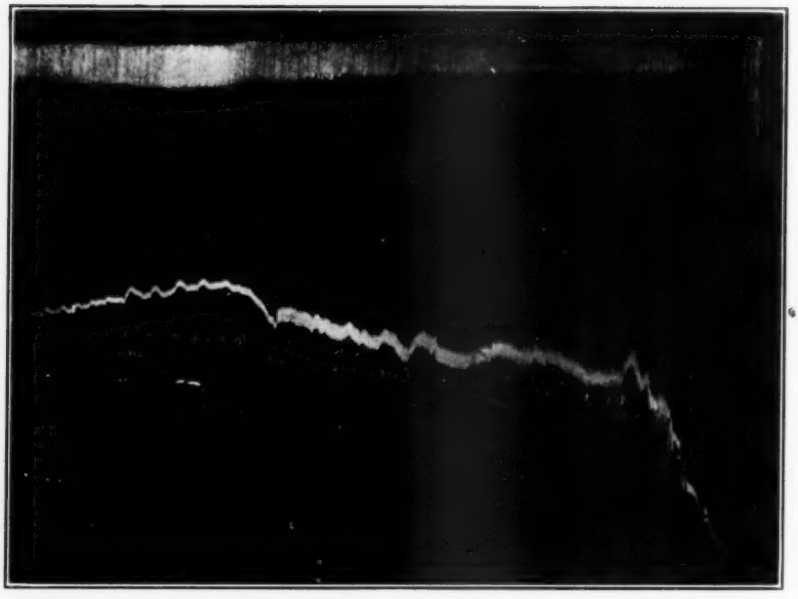

FIG. 3.—Showing effect of injections of a mixture of cobra venom and blood serum after 15-minute irradiation with Kromayer lamp.

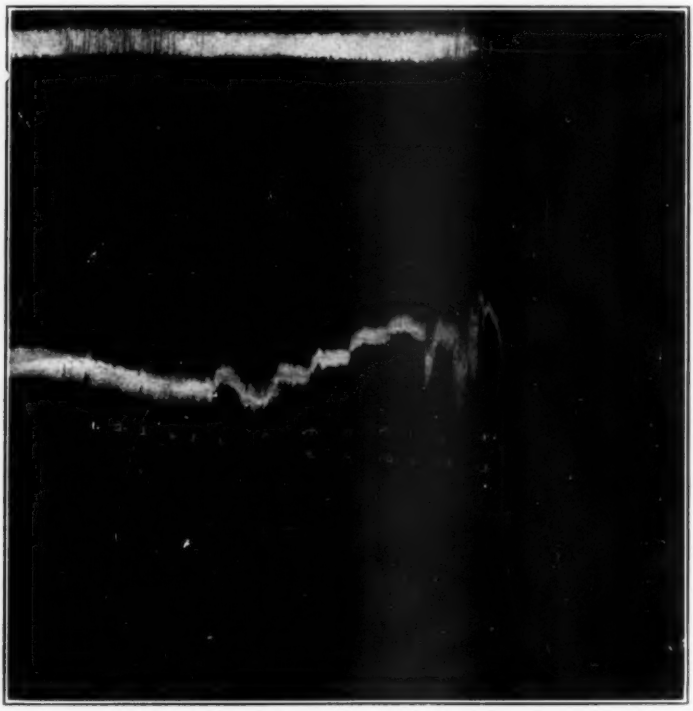

FIG. 4.—Showing effect of irradiation of cobra venom (containing no blood serum) with Kromayer lamp.

the effect of repeated, progressive injections of solutions of cobra venom, 1 to 10,000, into the femoral vein of a cat. The records indicate the effect on the respiration and circulation and also the minimal lethal dose per kilo weight required to kill the animals. It will be noted that in Fig. 2 the minimal lethal dose per kilo weight of the irradiated cobra venom injected was a little over 1 mg. In Fig. 3 is shown the effect of a similar solution of cobra venom, previously irradiated for 16 minutes by the Kromayer lamp. Here the minimal lethal dose was increased to 5 mg., indicating that marked detoxification had been produced. Fig. 4 illustrates the effect of a similar solution of cobra venom, to which a small quantity of blood serum had been added before irradiation was commenced. In this case the blood serum that had been added to the venom definitely protected it against the action of the ultraviolet rays, and the minimal lethal dose was 3.5 mg. per kilo weight of the animal.

Experiment of October 11, 1934.

(With Solutions in Thunberg Tubes, Each Containing 300 Mg. of Rat Muscle.)

Tube No. 1.

Three cc. of methylene blue solution + 3 cc. of saline + 0.5 cc. of cat serum.

Decolorized in 3 hours.

Tube No. 2.

Three cc. of methylene blue solution + 3 cc. of saline + a mixture of 0.5 cc. of cat serum and 5 mg. of cobra venom which had been previously irradiated with the Kromayer lamp for 15 minutes.

Oxidation completely inhibited. No decolorization in 24 hours.

Tube No. 3.

Three cc. of methylene blue solution + 3 cc. of saline + 0.5 cc. of cat serum + 5 mg. of cobra venom which had previously been irradiated alone with the Kromayer lamp for 15 minutes.

Decolorized in 5 hours.

TABLE 5.—EFFECT OF ROENTGEN RAYS AND RADIUM RADIATIONS ON COBRA VENOM.

Mouse No.	Dose injected, mg.	Treatment given doses of cobra venom administered.	Dead in.
1	0.1	Not irradiated	1 hr., 25 min.
2	0.1	Not irradiated	1 hr., 32 min.
3	0.1	Exposed to Roentgen rays, 500 Roentgen units	1 hr., 33 min.
4	0.1	Exposed to Roentgen rays, 500 Roentgen units	1 hr., 52 min.
5	0.1	Exposed to radium radiations, 1 gm. hr.	1 hr., 24 min.
6	0.1	Exposed to radium radiations, 1 gm. hr.	1 hr., 38 min.

Effect of Roentgen Rays and Radium Radiations. An opportunity was afforded the writer by Drs. C. F. Burnam and M. B. West, of the Howard A. Kelly Hospital, Baltimore, to treat specimens of cobra venom with Roentgen rays and radium. The results obtained are briefly summarized in Table 5. The Roentgen ray

dosage employed was 500 Roentgen units. The radium dosage was 1 gm. hour. The results obtained indicate that these powerful but very short ultraviolet rays produce little effect on the venoms exposed to them.

Discussion. The conclusions to which the present investigation points are clearly defined. Ultraviolet radiations were found to produce a rapid decrease in toxicity of snake venoms in aqueous solutions placed in quartz cells, the degree of deterioration being proportional to the time of exposure, as biologic experiments on both living plants and living animals indicated. In this respect the most effective ultraviolet rays were found to be those between 3000 and 4000 Ångström units. Even prolonged exposure to such longer ultraviolet rays as are filtered through a Wood filter, on the one hand, or to the shorter ultraviolet rays transmitted through a chlorin gas filter, on the other, produced little or no change in the activity of the venom solutions. Similarly, exposure to hard Roentgen rays and to radium radiations resulted in only a slight decrease in the activity of the venoms.

When snake venoms are injected into mice or rats and the animals are irradiated for curative purposes, however, the results are disappointing. The rapid onset of death indicates that there is no diminution in the virulence of the poison. Indeed, in many experiments the irradiation of animals previously injected with venom only hastened a lethal outcome. Only in exceptional cases was there any indication of a destructive action of ultraviolet rays on venom injected into the tissues of mice. In such cases the venom had been introduced in regions where absorption was poor, that is, by intradermal injection in the back. Experiments were also performed with mice to which other drugs were administered simultaneously with the venom solutions for the purpose of retarding absorption from the tissues. Such tests were made with injections of small quantities of epinephrin, which retards absorption through its powerful vasoconstricting action. Other experiments were made with injections of hypertensive solutions of sodium sulphate. In neither case was death of the animals delayed.

The great difference between the results obtained in experiments outside and inside the body, respectively, cannot be attributed altogether to poor absorption of the venoms from the tissues or to the lack of penetrating power on the part of ultraviolet rays. The experiments described above indicate definitely that certain body fluids, and particularly blood serum, exert a protective action on snake venoms against the effects of ultraviolet rays; and it is probably this mechanism which renders the therapeutic application of ultraviolet radiation futile. The most that can be expected is that such ultraviolet rays may be useful in snake poisoning when applied directly to opened wounds. When a patient is bitten by a reptile,

the usual procedure is to slash open the tissues at the seat of the bite and to apply suction or chemical antidotes to the wound. In such cases, irradiation with a mercury vapor lamp may be a useful therapeutic procedure, although it is a question whether the presence of body fluids may not interfere with the effectiveness of the ultraviolet rays. Irradiation of venom solutions in quartz containers may also prove to be a useful method of attenuating the poisons for the purpose of injection in suitable clinical cases where therapeutic administration of snake venoms is indicated.

Summary. 1. Exposure of snake venoms in solution to radiations of mercury vapor lamps produces progressive decrease in toxicity, as indicated by pharmacologic tests on living plants and animals.

2. The ultraviolet rays most effective in this respect lie in the region between 3000 and 4000 Ångström units, the longer and shorter ultraviolet rays being less effective.

3. Snake venoms exposed to Roentgen rays and radium radiations undergo but little change in toxicity.

4. Mice exposed to ultraviolet rays after previous injection of snake venom exhibit no diminution of susceptibility to this toxin and usually succumb more quickly than unirradiated animals injected with venom.

5. The difference between the effects produced by ultraviolet rays on snake venoms *in vivo* and in quartz containers, respectively, is due primarily to the protective action exerted by blood serum.

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EFFECTIVE TREATMENT OF ARACHNIDISM BY CALCIUM SALTS.

A PRELIMINARY REPORT.

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INVESTIGATION of the treatment of the black widow spider (Latrodectus mactans) bite has been going on since the serious results of the bite have been recognized, probably since the beginning of the 18th century. During the past 10 years this investigation has been more scientifically thorough and extensive; but it certainly has not produced any definite and easily accessible therapeutic measure which can be depended upon in all cases for the immediate and lasting relief of the extreme pain which most of the affected patients suffer. The search is indicated not only because of the severity of the pain and the mortality, but because of the relatively widespread existence of this spider. Cases have been reported in 32 states of this country, mostly in the southern half, also in South America and Australia, and with less frequency in other parts of the world.[1,2]

In the past, numerous therapeutic agents have been used, some more or less rational, but mostly without any such basis. Bogen[3] lists 60, such as morphin, whiskey, spirits of ammonia, atropin, magnesium sulphate, strychnin, calomel, castor oil, iodin, salicylates, hot applications, enemas, etc. In our experience, as in that of others,[1,4–17], morphin has been used with indifferent success when administered to adults even in large doses. The fallacy lies in the fact that it has no effect on the seat of the pain itself, but affords variable degrees of relief only by its depressant action on the central nervous system. Spinal fluid pressure is known to be increased but withdrawal of fluid has been found to give quite inconstant results.[1] Magnesium sulphate, intravenously, which probably acts by decreasing the cerebrospinal fluid pressure, has been used with more or less success, but the relief obtained is neither immediate nor complete.[1,4] Furthermore, considerable technical difficulty would be experienced in its administration to infants or small children. Convalescent serum[1,3,8,24] has been demonstrated to have little or no effect on victims of the venom.

The serum must be administered immediately after the patient has been bitten, which is impracticable, and one[2] of the proponents of its use has admitted that the course is unaltered except for being shortened by a day or two. Further discussion seems unwarranted for we have reviewed a large portion of the literature[3,5–23] dealing with cases of Latrodectus mactans bite and find that no treatment is of particular value.

We have attempted to develop some simple form of therapy which will insure early and lasting relief from the excruciating pain present in this condition.

The active principle of the venom has not, as yet, been definitely determined, but, as to its mode and place of action, it is quite generally accepted that the toxin directly stimulates the myoneural junctions or that it acts on the nerve endings.[2,8,13,25] To find a type of therapy which would have a direct depressant effect upon these structures would be ideal. As calcium apparently depresses the neuromuscular junctions[26] in muscle or is depressant to most nervous and muscular functions,[27] we selected calcium salts for the treatment of this condition.

We found that intravenous injections of 10% calcium chlorid gave instantaneous and prolonged relief of the pain, and at the same time produced immediate relaxation of the muscle spasm so commonly seen in these patients. However, calcium chlorid is not given thus without considerable danger. Its necrotic action on tissue outside a vein is only too well known. This danger is greatly magnified when its use is attempted in the treatment of children. Therefore, calcium gluconate (10 cc. of 10% solution, intravenously), which does not have this objectionable feature, was used and found to produce equally as spectacular results as the calcium chlorid. The intramuscular route, advisable for children, gave relief within a minute's time. Calcium lactate orally was ineffective as far as determined, probably because of its incomplete and slow absorption.

Case Reports. Case 1.—C. W., a white male, aged 16, was admitted at 6 P.M., October 26, 1934, having been bitten at 3 P.M. in the right shoulder region while lying under a car upon ground thickly covered with grass and weeds. The bite produced a sharp sting. About ½ hour later there was dull pain in the right shoulder, gradually becoming more severe and spreading to the chest and abdomen and then to the legs. Examination revealed the patient rolling from side to side because of the excruciating pain. The forehead was covered with perspiration. A red area, about 1 cm. in diameter, was visible at the site of the bite. Both pupils were dilated. Blood pressure was 160/70. Heart and lungs were normal. The abdomen revealed board-like rigidity, but no tenderness. Much pain was complained of in the extremities, but no tenderness or spasticity was elicited. Serological study was negative. At 6.20 P.M., before an intravenous injection of 20 cc. of 10% calcium chlorid could be completed, the pain and muscle spasm had entirely disappeared. At 10.45 P.M., pain returned in the legs and another 20-cc. intravenous injection was given. The next morning, at about 9 o'clock, the urinary bladder was found distended

two-thirds of the way to the umbilicus, but the patient soon voided without catheterization. The treatment was repeated at 2 P.M. and at 9.30 P.M. and on October 28 at 10 A.M., because of the return of pain in the lower extremities. Thereafter, until discharge, at 4 P.M., October 30, there was no further pain. Unfortunately, the patient did not search for the suspected black widow spider.

CASE 2.—C. G., a Mexican male, aged 16, was bitten on the scrotum at noon of November 1, 1934, while seated in an infrequently used toilet in the rear of a garage. Upon feeling the sting, the boy reached for the scrotum and pulled forth a spider which was later identified by a physician as being a black widow. Soon afterward, pains were experienced in the abdomen and back and then "everywheres," and later vomiting ensued. The patient could not sleep and was admitted, November 2, 1934, 9.30 A.M., still complaining of marked pain. He was sweating profusely; his eyes red and swollen. Heart and lungs were normal. The abdomen was rigid, but not board-like. At 11 A.M., 20 cc. of 10% calcium chlorid was given intravenously and the pain disappeared within 30 seconds. At 5.30 P.M., because of pain in the throat, 10 cc. of 10% calcium gluconate was administered intravenously and was repeated at 10 P.M. with instant relief. Examination of the throat before giving medication revealed no lesions. On the second day at 9 A.M., 5.45 P.M. and 8.30 P.M. and on the third day at 9.15 P.M., 10 cc. of 10% calcium gluconate was given intramuscularly on the return of pain. It was found that, except for a slight delay, calcium gluconate by this route relieved the pain as effectively as when given intravenously. On the second and third days, calcium lactate, 120 gr., twice daily, was given orally but was discontinued because of no apparent results. On the second day, 9 hours after any intravenous or oral administration of calcium, the blood was found to contain 12 mg. of calcium per 100 cc. of serum. Serologic studies were negative. The patient was discharged, November 6, relieved of all symptoms.

CASE 3.—H. T., a white male, aged 36, on November 18, 1934, about 7 P.M., on his back porch, felt something crawl down his back, and then experienced a burning pain in the right scapular region. In 10 minutes the upper back felt numb, followed by a tight feeling about the chest, and in turn severe lumbar pain, moderate abdominal pain and pains in the legs. The spider was later brought to us and identified as a black widow. On admission, at 10.30 P.M. of the same day, the patient was experiencing excruciating pains in the lumbar region and lower chest. The blood pressure was 150/100. The heart and lungs were normal. There was rigidity of the abdomen, but no tenderness. Serologic study was negative. When seen the next day, the man's pains were not severe, but at 6 P.M. he was found tossing and crying because of pain in both lower extremities and in the abdomen. Ten cc. of 10% calcium gluconate were given deep in the gluteal region, and within 1 minute the pain had entirely disappeared. Thereafter the pains were limited to the legs, but were not at all severe. However, another injection was given at noon, November 21, with total relief of the pain until discharge on November 23.

CASE 4.—C. H., a white female, aged 69, was bitten by a spider about 8 A.M., on November 6, 1934, on the back of the left hand while handling a pair of stockings she had just removed from her clothesline. Without any coaching whatever she described the creature, giving the characteristic features of a black widow spider. Almost at once there was pain in the hand which continued. An hour later, there was also pain in the axilla which became progressively worse. On admission, at 10.30 A.M., the patient did not seem to be in great pain. The blood pressure was 170/85. There was swelling and redness of the dorsum of the left hand and tenderness in the muscles of the arm, shoulder and pectoral regions, without any rigidity. The heart, lungs and abdomen were normal. The blood calcium

was 10.1 mg. per 100 cc. of blood serum and the blood serologic studies negative. By 2 P.M. the pain had increased so that the patient was found sitting on the side of the bed holding the left side of her chest and the left arm, having an agonizing expression. Calcium gluconate, 10 cc. of 10% solution, was given intramuscularly with almost immediate relief of the pain, although tenderness remained. There was no further pain and the redness and swelling of the hand gradually subsided before discharge on the morning of November 10.

CASE 5.—A white male, aged 28, was bitten by a black spider, on November 6, 1933, on the scrotum while tearing down an old barn. About 2 hours later he developed nausea, vomiting, profuse perspiration, excruciating generalized abdominal pain, pains in the thighs, legs, arms and forearms, and a feeling of tightness and suffocation about the chest and throat. He was unable to speak because of "tightness" in the masseter muscles. Admitted to St. Vincent's Hospital, at 9 P.M., November 7, 30 hours following the bite, he was found screaming with pain, and thrashing and rolling about the bed. The skin was hot and moist. Blood pressure was 160/95. The pulse was rapid but of good quality; temperature, 101° F.; respirations, 30. There was board-like rigidity of the abdomen, but no tenderness. The reflexes could not be accurately determined because of the extreme restlessness. The white blood count was 30,000, with 80% neutrophils. At 10 P.M., a 10-cc. ampule containing 1 gm. of calcium chlorid was given intravenously with immediate relief of the pain and total relaxation of the spastic muscles. Ten minutes later, the patient was sitting up in bed, smoking and drinking and complaining only of some aching in the feet and throat. Morphin sulphate, ¼ gr., was given hypodermically with sleep following. Because of a return of the pain, 7.30 A.M., the following day, another ampule of calcium chlorid was given with the same favorable results. Symptoms again returned, 9 P.M., November 9, when 1 gm. of calcium gluconate was taken orally followed by a hypodermic of morphin with relief of pain in 15 minutes. Three hours later it was necessary to repeat these same drugs and again at 2 P.M., November 10, with relief of pain 15 minutes later each time. The patient was discharged that evening symptomless.

Comment. It is evident from the cases cited that the calcium salt was responsible for the relief and that the time required depends on the method of administration, the intravenous method giving the most rapid results, and the intramuscular only slightly slower. In spite of the disappearance of the pain in Case 5 when calcium was given by mouth, we still believe it is not a desirable, and in fact a futile, route of administration, as shown in Case 2. In Case 5 morphin was given in conjunction.

The observation in Case 4 indicates that the symptoms in this malady are not due to a lowered calcium as in tetany for the serum calcium was within normal range.

Conclusions. 1. Latrodectus mactans and victims of their bite are common enough throughout the world to warrant search for a suitable form of therapy.

2. No remedies have heretofore been reported which produce certain, immediate and prolonged relief of pain.

3. Calcium depresses the myoneural junctions, which, it is believed, are stimulated by the venom.

4. Calcium in the form of calcium gluconate is chosen because of its ease of administration to children by the intramuscular route

and because it is practically without hazard when given intravenously.

5. A limited number of cases are reported to show its efficacy in producing real, immediate and prolonged relief.

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(Titles have been omitted for sake of brevity.)

HYPOPROTEINEMIC NEPHROSIS AND ITS TREATMENT WITH ACACIA.

Report of Two "Cured" Cases.

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Various attempts have been made to classify lipoid nephrosis as a renal disease; but lipoid nephrosis will be satisfactorily defined and classified only after its ultimate etiology and pathologic physiol-

ogy are fully known. Clinically, this condition is easily recognized; nevertheless the diagnosis of lipoid nephrosis should be made with the reservation that some of the cases so diagnosed will prove, in the last analysis, to be cases in which the kidneys show insignificant pathologic lesions. This nephrosis syndrome, characterized by edema or anasarca, may also be induced by a hypoproteinemia following protein starvation and protein loss as in chronic diarrhea. Leiter[1] estimated that true lipoid nephrosis occurs in 1 to 5% of all non-suppurative renal diseases.

Diagnostic Criteria. 1. History of onset with acute infection. Nephrosis generally occurs in the young.

2. Severe albuminuria, oliguria, ability to concentrate urine, absence of hematuria.

3. Edema or anasarca.

4. Lipemia; hypercholesterolemia.

5. Low serum albumin, high serum globulin, a reversal of the normal albumin-globulin ratio of the blood serum. Serum albumin below the critical level at which edema begins.

6. Doubly refractile lipoids in the urine.

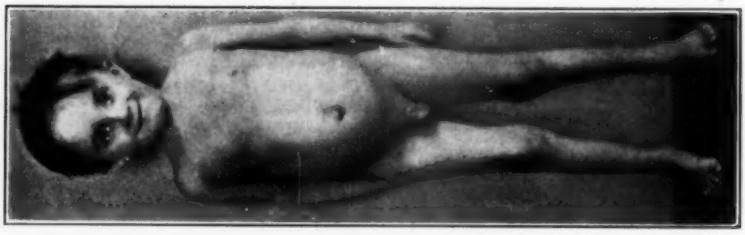
7. Clear transudate in extremities; opaque, milky ascitic fluid.

8. Systemic (pneumococcic) infection in the terminal stages of the disease.

Pathology. Epstein[2] has designated nephrosis as a "diabetes albuminuricus," emphasizing the metabolic origin of this condition. He explained the edema on the basis of reduced plasma protein. Leiter[3] contrasts and correlates nephrosis with chronic glomerulonephritis. His experimental studies led him to the conclusion that loss of serum proteins with its resultant hypoproteinemia is the underlying cause of the edema. Amberg[4] is of the opinion that the comparatively slight structural changes in the kidneys in chronic nephrosis exclude it from being classified with renal disease, and that depletion in blood proteins alone is not the underlying cause of the edema. He believes that there must be certain chemical disturbances behind all this. Bell,[5] leaning upon Senator's conception of glomerulonephritis, looks upon chronic nephrosis as a nephrotic type of glomerulonephritis, and he believes that the primary cause in both nephrosis and nephritis resides in toxic injury to the renal capillaries. Hitzrot and Read[6] see very slight or no relationship between nephrosis and glomerulonephritis. Moschcowitz[7] holds that "nephrosis cannot be classified as a disease because it has multiform backgrounds in morbid anatomy," and that the fundamental cause of the edema in these conditions is hypoproteinemia.

After due consideration of these views, some of which are conflicting, it is perhaps best that, for the present, the clinician look upon nephrosis simply as a well-defined clinical syndrome. It is evident that the glomeruli at times do show histologic changes. It

is likewise true that such changes are probably not more extensive than could be found in other tissues in a well-marked case of this disease state. It should be recalled here that edema of itself is not a sequel to injury or destruction of renal tissue.



On discharge.

Before acacia.

Two days after acacia.

Three weeks after acacia.

On the whole, available evidence favors the view which has been acceptable to Epstein, Leiter, Moschcowitz and others that loss of serum protein through severe albuminuria causes a fall in osmotic

pressure with resulting edema. Leiter[1] and later Moschcowitz[7] noted the fact that in hypoproteinemia it is loss of the albumin fraction which is important in edema production. The part played by the cell is not yet understood, neither are the chemical or physicochemical changes that the cell must undergo to permit the change in osmotic pressure.

Present Experience. Our main interest here is in the striking results obtained in the treatment of 2 patients by intravenous injections of acacia, as advocated in this country by Hartmann, Senn, Nelson and Perley.[8] Acacia intravenously raises the colloidal osmotic pressure of the blood plasma toward the normal. After a preliminary smaller dose, it may be given to establish a 2% concentration in the plasma, which concentration is obtained by administering 1 gm. per kilo body weight. We used a 30% solution of acacia with 4.5% sodium chlorid solution, which should be a clear pale yellow. Darker solutions may cause reactions and should be avoided. This acacia solution is diluted with normal saline to a total volume of 500 cc. and injected slowly.

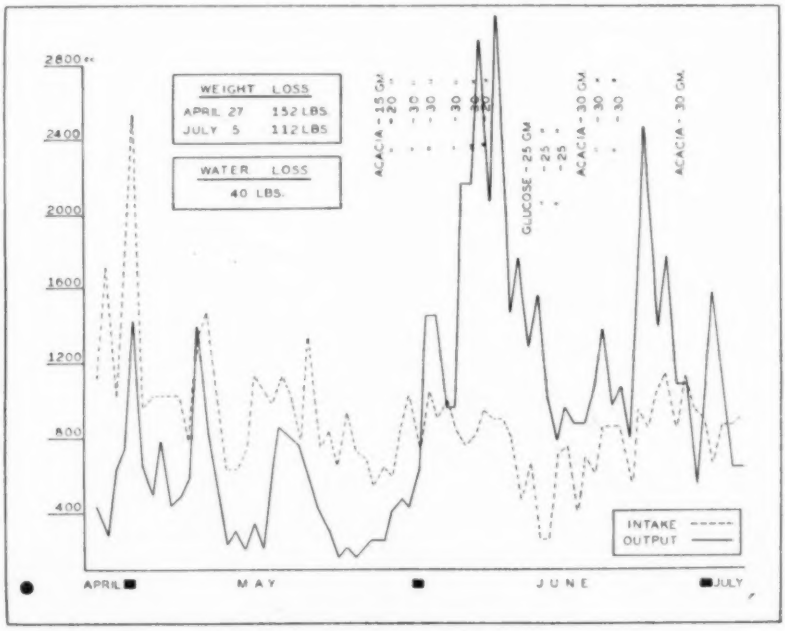


CHART 1.—Intake and output—Case 1.

CASE 1.—(Barach.) Mary Louise S., aged 20, admitted to the hospital, April 26, 1933. Her family history was negative. Her past history included an appendectomy 5 years ago, tonsillectomy 4 years ago and menstrual irregularity for 1 year.

Present Illness. The patient was diagnosed and treated as a case of nephritis, with a heavy cloud of albumin, for 1 year. Six months ago, following an attack of "influenza," she developed edema of the ankles and feet which gradually culminated in a generalized edema. She had been confined to bed since that time. For the past 4 months, she has had recurring nausea and vomiting, orthopnea, facial edema and anasarca. The case seemed quite typical and a clinical diagnosis of chronic nephrosis was made at the time of the consultation with her attending physician. Following this, she was hospitalized.

Clinical Findings. There was a generalized anasarca, including edema of the face and arms, ascites and massive edema of the lower extremities. There was oliguria and severe albuminuria. The serum albumin and total serum protein were low while the serum globulin was high. Whereas edema may develop when the daily loss of protein reaches 1 gm. per liter per day,

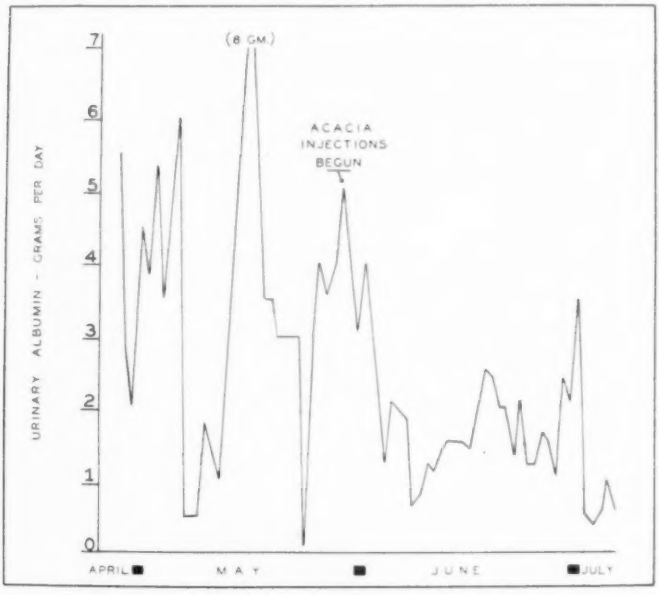


CHART 2.—Urinary albumin—Case 1.

this patient's loss of protein up to the time of the acacia varied between 1.5 and 8 gm. daily. Hypercholesterolemia was marked. At one tap, 3100 cc. of milky ascitic fluid were obtained and 3 weeks later 6100 cc. were removed. A secondary anemia was found. Blood chemistry, other than serum protein, was insignificant. Phenolphthalein output was high and glucose tolerance was normal. Table 1 gives the detailed studies of this case.

Treatment—Diet. To meet the caloric requirement, a diet of carbohydrate, 120 gm., protein, 52 gm., and fat, 70 gm., was ordered, with low salt. The patient was kept on this diet for 1 month. During the first month there was no improvement. A Carrell diet consisting of 800 cc. of milk daily was instituted for 5 days. This was followed by oliguria, her condition was aggravated and we abandoned the Carrell diet. Following this, the patient's diet was adjusted to 1.5 gm. protein per kilo body weight.

Half of this protein was given in the form of gelatin. No effects were noted over a period of 4 weeks.

Medication. Desiccated thyroid extract (1 to 5 grains, t.i.d.) was not effective and was discontinued. Potassium bitartrate in large and small doses was not effective. Daily injections of glucose, 10 to 25%, intravenously, did not produce diuresis; its effects were neither good nor bad. Calcium lactate was given by mouth and seemed ineffective. Magnesium sulphate (½ ounce daily) produced free bowel movements with elimination of a certain amount of liquid.

Acacia. None of our therapeutic measures were effective up to the time of the first injection of acacia. Altogether 11 injections of acacia were given, making a total of 295 gm. in 4 weeks. One intravenous injection of 15 gm., 2 of 20 gm. and 8 of 30 gm. each were given at 1- or 2-day intervals. For the anemia, weekly injections of liver extract intramuscularly seemed to induce a favorable response.

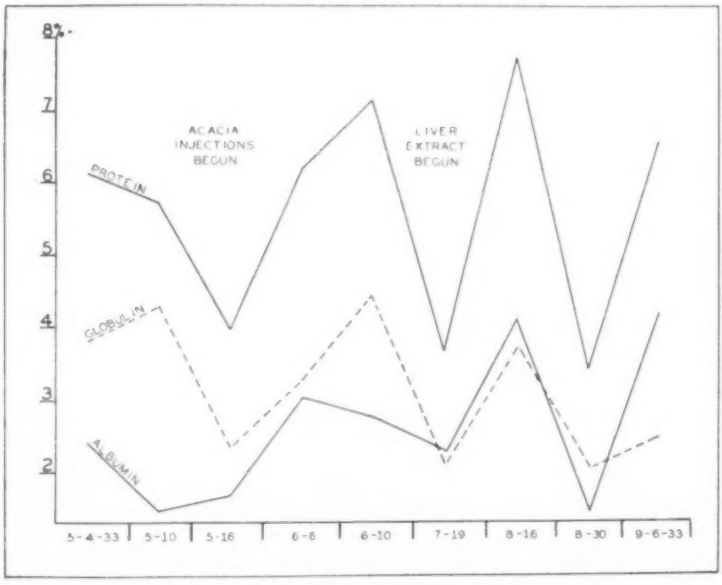


CHART. 3—Serum protein—Case 1.

Course and Summary. We have here a typical case of chronic nephrosis which responded satisfactorily only after intravenous injections of acacia were begun. Diuresis was striking, as is shown in Chart I. For the first time in 7 months, the patient showed clinical improvement. The patient received in all 11 intravenous injections (295 gm.) of acacia during her stay of 72 days in the hospital. During this time there was a loss of 40 pounds in body weight, most of which was water loss. When she was first allowed out of bed there was still considerable edema at the ankles, but this subsided gradually. Six weeks after she left the hospital, there was no visible edema and her general condition was good. The urine still showed a cloud of albumin, otherwise she showed evidences of a clinical recovery.

On December 1, 1934, 2½ years after the beginning of this disease and

1½ years after the acacia injections were begun, this patient is to all appearances in good health. She married 7 months ago and is now 6 months pregnant. She is in good health and there is no edema. Her serum protein is 9.25%, serum albumin, 5.52%, and serum globulin, 3.73%. The urine is negative for albumin. All of this is evidence of a return to normal.

TABLE 1.—PROTOCOL OF CASE 1.

	4/26.	5/4.	5/10.	5/16.	5/20.	6/6.	6/10.	6/20.	7/19.	8/9.	8/16.	8/30.	9/6.
Body weight (pounds)	152	151	...	...	147	140	121½	115	120	119½	119	119¼	124½
Serum protein (%)	..	6.09	5.67	3.90	...	6.10	7.06	...	3.59	..	7.65	3.31	6.50
Serum albumin (%)	..	2.35	1.40	1.61	...	2.93	2.69	...	2.00	...	4.01	1.36	4.10
Serum globulin (%)	..	3.74	4.27	2.29	...	3.17	4.37	...	1.59	...	3.64	1.95	2.40
Blood urea (mgm.)	...	...	...	...	...	...	10.5						
Blood N.P.N. "	28.5	28.5	...	...	...	...	29.6	29.6	...	...	...	...	31.4
Blood creatinin "	2.2	...	...	...	...	...	1.8	...	...	...	...	...	1.6
Blood sugar "	115	65	...	...	...	...	...	90.9	...	...	...	...	87
Blood chlorid "	500	...	...	...	...	...	663	534	...	...	...	...	478.5
Blood cholesterol "	..	...	428.6	428.6	...	...	279	262	...	...	...	...	300
Blood calcium "	..	...	...	...	7.2	...	...	...	...	...	...	...	9.7
Icterus index	...	21.4	...	...	...	...	...	...	...	...	...	...	13
Hemoglobin (%)	80	...	...	...	52	56	...	63	55.8	84.1	...	87.2	
R. B. C. (millions)	4.1	...	...	...	2.52	2.94	...	6.25	2.9	4.38	...	5.08	
W. B. C. (thousands)	11.1	...	...	...	5.2	7.0	...	9.6	5.8				
Urinary urea (gm. per liter)	4	...	...	...	...	9	...	...	...	...	...	13.8	
Urinary N.P.N. (gm. per liter)	1.6	...	...	...	...	6.05							
Urinary chlorid (gm. per liter)	..	...	...	...	...	...	...	...	7.0	6.5	...	15.0	
Urinary albumin (gm. per 24 hours)	5.5	3.5	1.8	8.0	3.0	1.9	1.2	2.0	4.5	7.0	5.2	5.6	3.0
P. S. P. test	76%												
Glucose tolerance	...	...	...	...	...	...	...	Norm.					

CASE 2.—(Boyd.) Robert O'M., aged 4 years, 3 months, entered the Children's Hospital on August 11, 1932. There was a history of rickets and bronchopneumonia at 7 months and tonsillectomy at 3 years and 3 months of age.

Present Illness. At the time of his tonsillectomy, the family physician had diagnosed kidney trouble, looking forward to improvement after the tonsillectomy. Six months later there was morning puffiness under the eyes. This became worse and generalized edema gradually developed. One year after the albuminuria was first discovered, there was ascites. At this time the patient was hospitalized.

Clinical Findings. At the time of entrance to the hospital, there was weakness, anorexia and swelling of the abdomen, genitalia and lower extremities. The blood pressure was 103/70, eye grounds were negative and the sinuses, ears, nose and throat were negative. The Wassermann reaction was negative. The urine showed a heavy cloud of albumin with casts and doubly refractile lipoids. His blood chemistry was negative except for serum protein, as shown in Table 2. There was anemia and with this a periodic leukocytosis.

Treatment—Diet. The diet was high in protein. Fluid restriction had no beneficial effects.

Medication. Hot and dry packs were ineffectual. Magnesium sulphate and jalap were used for catharsis. Thyroid (¼ grain, t.i.d., for 5 to 6 weeks) was not effective. Urea (in doses of 5 to 15 grains, t.i.d.) was given throughout the hospital stay. Calcium gluconate was given, 10 cc., intravenously, for 4 injections. Salyrgan was given in doses of ½ ampule, but the results were not favorable. An autogenous vaccine of a non-hemolytic streptococcus was cultured from the urine. This was inoculated into a suitable

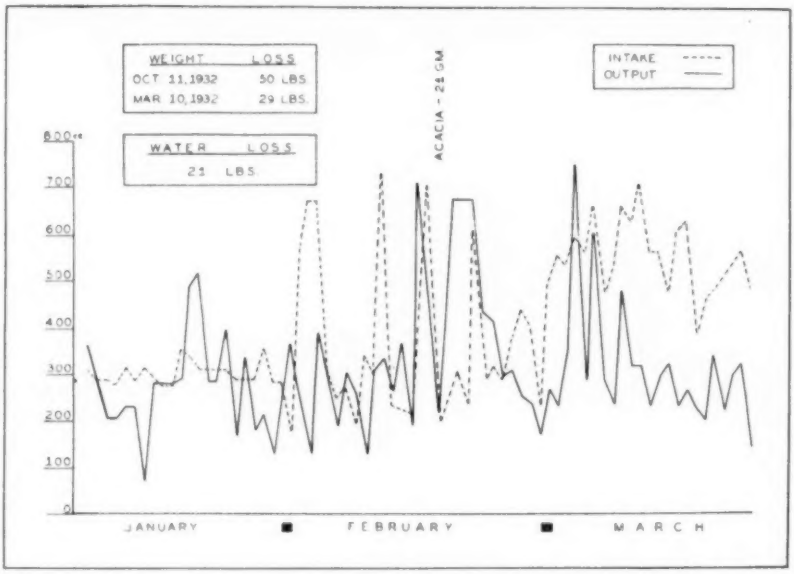


CHART 4.—Intake and output—Case 2.

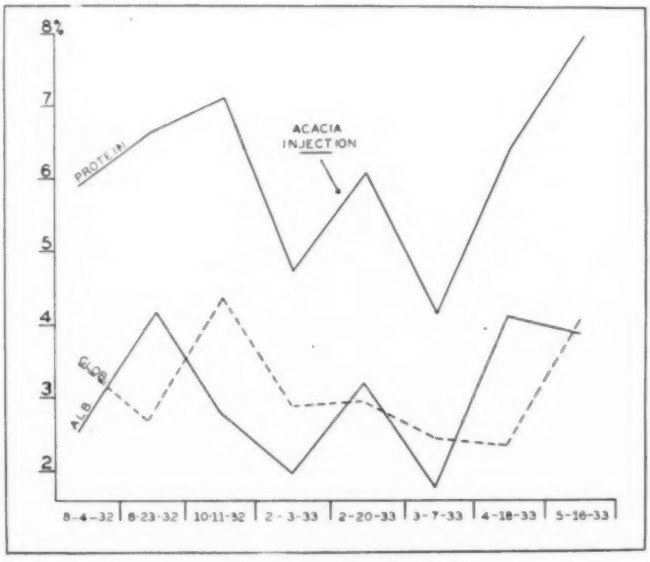


CHART 5.—Serum protein—Case 2.

donor and several transfusions given to the patient. It may be said that none of these therapeutic measures produced a striking result.

Acacia. On February 18, 1933, 7 months after entrance into the hospital, 21 gm. of acacia was given intravenously. Following this there was a striking diuresis which was followed by daily improvement in the patient's general condition. Up to this time the patient had been in the hospital 7 months without visible improvement regardless of the various treatments attempted.

Course and Summary. Three months after the acacia injection, he was well enough to be discharged from the hospital. On December 8, 1934, almost 22 months after the acacia injection, the patient is living a normal boy's life and is apparently in good health. His urine still shows some albumin but his serum protein is 8.37% and his general condition indicates a clinical recovery.

TABLE 2.—PROTOCOL OF CASE 2.

	7/7.	7/14.	8/4.	8/23.	9/20.	10/11.	11/1.	1/11.	2/3.	2/20.	3/7.	4/18.	5/16.	10/16.
Body wt. (lbs.)	50	....	....	....	....	....	....	50	45	35½	29½			42
Serum protein	....	....	5.85	6.58	..	7.05	....	....	4.70	5.04	4.10	6.38	7.95	7.65
Serum albumin	....	....	2.45	3.98	..	2.75	....	....	1.90	3.14	1.70	4.08	3.90	4.00
Serum globulin	....	....	3.40	2.60	..	4.30	....	....	2.80	2.90	2.40	2.30	4.05	3.65
Blood urea	....	....	11.6	7.6										
Blood N.P.N.	46	42.8	36.1	30.6	25.0	..	....	....	35.0	..	27.3	42.8	35.5	
Blood creatinin	1.4	1.7	..	1.0	..	..	....	....	1.0					
Blood sugar	....	117	..	....	..	96.1								
Blood chlorids	....	515												
Hemoglobin, %	77	....	83	....	77	..	60	91	....	55	50	..	64	78.9
R.B.C. (m'l'ns)	4.2	....	4.25	....	3.95	..	3.15	4.65	....	2.9	2.7	..	3.35	4.65
W.B.C. (th's'd)	16.2	....	12.2	....	9.9	..	12.1	9.1	....	32.8	12.8	..	9.6	13.3
P.S.P. test	Trace													
Doubly refractile lipoids	....	....	..	....	..	..	11/3 11/4							
Urinary alb.	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++	++	0.23

Summary and Conclusions. A case of chronic lipoid nephrosis in a young woman, aged 20, and one in a boy, aged 4, are reviewed. Neither patient showed evidences of improvement until acacia was given intravenously. One case received 11 injections, totaling 295 gm. acacia, the other required only 1 injection to start the diuresis and bring about a clinical recovery. In both patients there was a striking diuresis following the acacia injections. Systemic reactions from the acacia injections were mild and without ill-effects. Intravenous injections of acacia as used here have produced the most striking therapeutic effects that we have ever seen in chronic nephrosis.

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THE EFFECT OF EQUIVALENT AMOUNTS OF DEXTROSE AND STARCH ON GLYCEMIA AND GLYCOSURIA IN DIABETICS.*

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The question of the extent of glycemia and glycosuria produced in patients suffering from diabetes mellitus by the ingestion of dextrose and of an equivalent amount of starch has received but little study.

Allen,[1] in a paper on the effects of carbohydrate diets on diabetes, makes the following statement: "Numerous observations have made it evident that glucose brings on glycosuria and diabetes more actively than starch. The difference is not merely one of quantity, for the addition of 50 or 100 gm. of glucose is sometimes effective when no amount of bread feeding avails for glycosuria. The reason for the readier glycosuria from glucose lies evidently in its quicker absorption, and if distributed in sufficiently small doses throughout the day it would presumably be assimilated as well as starch, as Klemperer showed in human patients. The most important point here is that the sudden glucose flood with its attendant glycosuria is more injurious to the pancreatic function than the more gradual and prolonged labor imposed by starch. It may thus be inferred that sugar is a more dangerous food for human beings with any predisposition to diabetes than is starch." He states further: "In the early stage glucose is more powerful than starch in producing diabetes, and animals which are progressing toward complete recovery on starch diet can be sent into hopeless diabetes by admixture of glucose."

As far as normal individuals are concerned, Howell[2] states that the more slowly converted starch may be eaten in larger amounts than the rapidly absorbed sugar without raising the percentage of blood sugar above normal. He further points out that during the 4 or 5 hours required for starch digestion the entire quantity of blood in the body goes through the mesenteric arteries many times, and it is probable that even in the portal vein the quantity of sugar is never much above normal. As any small excess is largely held back by the liver cells, systemic hyperglycemia does not occur.

It has been shown by MacLean,[3] and also by Rosenthal and Ziegler,[4] that the rise in the concentration of the blood sugar in

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normal individuals after the ingestion of equivalent amounts of dextrose and starch is identical.

In this paper the results of experiments on the influence of the ingestion of dextrose and of an equivalent amount of starch on glycemia and glycosuria in patients suffering from diabetes mellitus will be reported.

Method. Experiments were performed on 21 diabetics. To 10 of them 100 gm. of dextrose, in a 20% aqueous solution, were given in the morning after a fast of 14 hours. Blood (venous) specimens were taken at the "fasting level" immediately before ingestion, 45 minutes and 2 hours after the ingestion of dextrose. The sugar content of the blood was determined by the Folin-Wu method. The urine was collected at the end of 45 minutes and 2 hours after ingestion of the dextrose, and its sugar content determined by Benedict's method.

Two days later, also in the morning after a fast of 14 hours, 90 gm. of starch* were given. The blood was taken and the urine collected at the same periods as when dextrose was given. In the interval between tests the patients were on their customary diets. Those who had been taking insulin continued to do so.

The same procedure was carried out on 11 other diabetics with this important difference, namely, that the starch was given first and the dextrose 2 days later.

TABLE 1.—CONCENTRATION OF DEXTROSE IN THE BLOOD AND QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 100 GM. OF DEXTROSE AND 90 GM. OF STARCH.

(In this series of cases the dextrose was given first and the starch 2 days later.)

Case No.	Blood sugar (mg. per 100 cc. of blood).						Urine sugar (gm.).					
	Fasting level.		45 minutes post cibum.		2 hours post cibum.		0 to 45 minutes post cibum.		45 minutes to 2 hours post cibum.		Total, 0 to 2 hours post cibum.	
	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.
1	333	326	508	500	576	454	10.8	11.6	32.0	24.8	42.8	36.4
2	306	375	460	546	546	508	2.7	11.3	21.1	19.6	23.9	30.9
3	375	395	500	600	556	682	4.8	5.5	13.5	22.7	18.3	28.2
4	214	230	344	374	410	380	5.0	6.8	13.2	16.0	18.2	22.8
5	170	196	208	272	410	384	0.12	0.67	2.9	5.6	3.0	6.2
6	272	222	460	405	556	390	4.2	2.8	15.7	13.9	19.9	16.7
7	294	303	468	405	680	600	5.7	5.3	11.5	12.9	17.2	18.2
8	300	332	468	500	556	546	5.2	6.0	13.5	16.3	18.8	22.4
9	272	318	566	422	468	492	3.1	1.4	13.8	15.0	16.9	16.4
10	221	280	404	428	600	566	1.7	2.0	14.1	14.3	15.9	16.3
Means	275.7	297.7	438.6	445.2	535.8	500.2	4.34	5.34	15.14	16.12	19.48	21.46
*Difference between means	22.0		6.6		35.6		1.0		0.98		1.98	

* The elementary formula for starch is $(C_6H_{10}O_5)$ with a molecular weight of n(162). The molecular weight of dextrose $(C_6H_{12}O_6)$ is 180. The complete hydrolysis of 90 gm. of starch yields 100 gm. of dextrose. In this experiment the starch was given in the following form:

	Total, gm.	Carbohydrate, gm.
Potato	150	30.0
Barley	30	22.4
Rice	30	22.4
Bread (toast)	30	15.0
		89.8

The starch was thoroughly cooked or baked, for raw starch is hardly acted upon by either salivary or pancreatic diastase.

Analysis of Results. In Table 1 are recorded the concentrations of blood sugar and amounts of dextrose in the urine after the ingestion of equivalent amounts of dextrose and starch, where the dextrose was ingested first. Statistical analysis* (Table 1*a*) does not

TABLE 1*a*.—DIFFERENCES IN THE CONCENTRATION OF DEXTROSE IN THE BLOOD AND THE QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 100 GM. OF DEXTROSE AND 90 GM. OF STARCH.
(Where dextrose is ingested first and starch 2 days later.)

Case No.	Blood sugar.†			Urine sugar.†		
	Fasting level.	45 mins. post cibum.	2 hrs. post cibum.	0-45 mins. post cibum.	45 mins. to 2 hrs. post cibum.	Total, 0-2 hrs. post cibum.
1	−7	−8	−122	+0.8	−7.1	−6.4
2	+69	+86	−38	+8.6	−1.5	+7.1
3	+20	+100	+126	+0.7	+9.2	+9.9
4	+16	+30	−30	+1.9	+2.8	+4.6
5	+26	+64	−26	+0.5	+2.7	+3.3
6	−50	−55	−166	−1.4	−1.8	−3.2
7	+9	−63	−80	−0.4	+1.3	+0.9
8	+32	+32	−10	+0.8	+2.8	+3.7
9	+46	−144	+24	−1.7	+1.2	−0.5
10	+59	+24	−34	+0.3	+0.2	+0.5
Mean difference ($\bar{x}$)	+22	+6.6	−35.6	+1.00	+0.99	+1.99
n'	10	10	10	10	10	10
$\frac{S}{\sqrt{n'}}$	10.80	23.89	25.14	0.905	0.882	1.512
t	2.037	2.076	1.417	1.105	1.118	1.314
P	0.076	0.79	0.19	0.30	0.29	0.22

* The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, 3d ed., London, Oliver and Boyd p. 104, 1930). The principle of the method is first to calculate the mean differences between the results obtained with two different experimental procedures. According to Fisher's method, whether or not the difference is significant, is determined as follows: A certain statistical value t is calculated from the data with the aid of a formula given below. Then taking into account the number of cases in the series a value P is derived by consulting tables in Fisher's book. P represents the frequency with which a value of t (sic. N.B., points) greater than the one obtained in the study could be found purely as a result of chance alone. The convention is to assume that when P is less than 0.05 the observed difference is significant.

For example, let us consider the results for the fasting blood sugar level. The mean difference, designated by $\bar{x}$, is in this instance +22, the plus sign indicating that the value is higher after the administration of starch. The value of t is derived as follows:

$$\frac{S^2}{n'} = \frac{1}{n'(n'-1)}\left[\Sigma x' - n'\bar{x}^2\right] = \frac{1}{10 \times 9}\left[\Sigma x^2 - 10(22.0)^2\right] = 116.64$$

$$t = \frac{x\sqrt{n'}}{S} = \frac{22.0}{10.8} = 2.037$$

If now the table in Fisher's book is consulted it is found (when $n = 9$, where $n = n' - 1$, n' being the number of cases in the series, and when $t = 2.037$) by interpolation that $P = 0.076$. Hence, by the convention referred to above the difference found is not considered significant. This holds true for all the other columns in Table 1.

† The sign of the difference was taken as positive when the values in the experiment with starch were larger, and as negative when the values with dextrose were larger.

reveal any significant differences in the mean concentrations of the dextrose in the blood at all levels. Also, the quantities of dextrose excreted in the urine are almost identical.

It might be argued that the giving of 100 gm. of dextrose caused a reduction in tolerance so that the blood sugar curve when starch was given was higher than it otherwise would have been. One of us (M. W.)[5] has performed 2 dextrose tolerance tests within a period of 2 days on each of 30 diabetics, using 100 gm. of dextrose as the test dose. Careful study of their tolerance before and after this procedure did not reveal the slightest depreciation of their capacity to utilize carbohydrates.

To answer this objection more directly, another series of cases was studied in which the starch was given first and the dextrose 2 days later. The results in this series (Tables 2 and 2*a*) strikingly confirm the validity of the conclusions drawn from the previous study. In fact, the mean differences obtained here are even smaller than in the first experiment.

TABLE 2.—CONCENTRATION OF DEXTROSE IN THE BLOOD AND QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 90 GM. OF STARCH AND 100 GM. OF DEXTROSE.

(In this series of cases the starch was given first and the dextrose 2 days later.)

Case No.	Blood sugar (mg. per 100 cc. of blood).						Urine sugar (gm.).	
	Fasting level.		45 minutes post cibum.		2 hours post cibum.		Total, 0 to 2 hours post cibum.	
	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.
1	256	330	424	504	436	525	21.2	16.57
2	304	372	386	480	554	533	33.2	29.4
3	320	400	499	512	546	586	33.0	31.9
4	296	267	432	364	500	410	8.0	8.3
5	298	307	518	439	546	592	10.9	7.8
6	284	251	486	414	570	441	18.7	10.7
7	334	318	498	480	562	546	4.5	12.7
8	267	270	435	440	520	606	18.9	17.1
9	310	263	476	444	...	...	3.9	4.5
10	200	238	308	460	356	534	6.8	12.0
11	244	239	435	416	435	488	17.9	17.3
Means	283.0	295.7	445.2	450.3	502.7	526.1	16.09	16.57
Difference between means	12.72		5.09		23.4		0.48	

A second possible objection is that in the first series the concentration of dextrose in the blood, though lower at the "fasting level," was higher at the "2-hour level" when dextrose was given. Hence, when the rise in the concentration of dextrose in the blood is considered it is conceivable that the differences might be significant.

For that reason a special statistical analysis was made of the difference in rise from the "fasting level" to the "2-hour level." In the first series (where dextrose is given first and starch 2 days later), it was found that P = 0.021, a value less than the conventional limit of significance, which is 0.05. However, the value is not low enough to rule out the possibility of coincidence. This is borne out by a similar analysis of the second series (where starch is given first and dextrose 2 days later), where it was found that P = 0.84, a value which indicates that the rises in concentration of dextrose in the blood were practically identical.

TABLE 2a.—DIFFERENCES IN THE CONCENTRATION OF DEXTROSE IN THE BLOOD AND THE QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 90 GM. OF STARCH AND 100 GM. OF DEXTROSE.
(Where starch is ingested first and dextrose 2 days later.)

Case No.	Blood sugar.*			Urine sugar.*
	Fasting level.	45 minutes post cibum.	2 hours post cibum.	Total, 0 to 2 hours post cibum.
1	−74	−80	−89	−9.4
2	−68	−94	+21	+3.8
3	−80	−13	−40	+1.1
4	+31	+68	+90	+0.3
5	−9	+79	−46	+3.1
6	+33	+72	+129	+8.0
7	+16	+18	+16	−8.2
8	−3	−5	−86	+1.8
9	+47	+32	....	−0.6
10	−38	−152	−176	−5.2
11	+5	+19	−53	+0.6
Mean difference $\bar{x}$	−12.72	−5.09	−23.4	−0.48
n'	11	11	10	11
$\frac{s}{\sqrt{n'}}$	13.75	22.56	28.44	1.57
t	0.926	0.224	0.823	0.306
P	0.38	0.83	0.43	0.77

* The sign of the difference was taken as positive when the values in the experiment with starch were larger, and as negative when the values with dextrose were larger.

Comments. As stated above, it is the contention of Allen, which is accepted by Joslin,[6] that dextrose brings on glycosuria and diabetes more actively than starch and that the sudden dextrose flood when dextrose is ingested is more injurious to the pancreatic function than the more gradual and prolonged labor imposed by starch. The findings made by us offer direct proof that such is not the case. *The glycemia and glycosuria after the ingestion of dextrose and of an equivalent amount of starch by diabetics are not significantly different.* Dextrose, therefore, is no more injurious to the diabetic than starch.

Conclusions.* 1. In patients suffering from diabetes mellitus, the glycemia and glycosuria after the ingestion of dextrose and of an equivalent amount of starch do not differ significantly.

2. It may be then concluded that from this point of view dextrose is no more harmful to the diabetic than starch.

We are indebted to Dr. Alexander S. Wiener for statistical analysis of the data.

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* It is of course obvious that administration of less excessive amounts of dextrose and starch might bring out differences, not apparent here, which would negate the conclusions drawn in this paper.—THE EDITORS.

DERMATITIS GANGRENOSA.

A COMPLICATION OF DIABETES MELLITUS.

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GANGRENE in diabetes is ordinarily confined to the lower extremities and is of a progressive nature. Usually it is associated with marked degenerative changes in the peripheral vascular system with obliteration of the blood supply to the involved part. Superficial lesions of the skin without evidence of arteriosclerosis, trauma or infection are rare. In the case reported here there was complete destruction of the superficial and subcutaneous layers of the skin with necrosis and gangrene without any evidence of peripheral atherosclerosis. To this the term "Dermatitis Gangrenosa" has been applied.

Case Report. A white female, aged 40, a known diabetic for 3 years, was admitted to the Vanderbilt University Hospital October 8, 1931, after being unconscious for 14 hours following the ingestion of a heavy carbohydrate meal. Except for the typical diabetic coma the examination was essentially negative. The blood sugar was 570 mg., the urine showed 30% glucose and contained acetone and diacetic acid. The usual treatment for diabetic coma was given and within 6 hours she regained consciousness. The following day she was still somewhat drowsy, the urine showed 2% glucose and no acetone bodies. Physical examination revealed over the right kidney area posteriorly a huge bleb, surrounded by an area of edema, filled with a yellowish watery material. There were similar lesions on the posterior surface of both legs. None of these was painful. The distribution of the blebs over the lower extremities, seemed to be only over

those areas where pressure had been made at points where the legs had been crossed. Several theories of the cause of these blebs were considered. First, an allergic reaction to insulin; second, trophic changes as a complication of the diabetes mellitus; and third, a vascular disturbance of an obliterating type with the lesions appearing at pressure points.

The lesions became more widespread with a scattered distribution over the back and the posterior surface of the thighs and legs. The first bleb ruptured and new ones formed. Beef insulin was substituted for pork insulin and calcium chlorid was given but the blebs continued to appear. On October 11, 40 hours after the onset of these lesions it was noticed that superficial ulcers formed at the site of the blebs and that there was a necrosis of the skin and some ecchymosis around the necrotic areas. On the back of both thighs, on the back of the right calf and on the inner side of the left calf particularly over the area where the legs crossed each other there appeared sharply circumscribed superficial areas of tissue destruction

FIG. 1.—The lesions of the skin showing the blebs, the superficial ulcers and necrosis of the skin.

which over most of these areas had gone on to gangrene. They were sharply circumscribed. The gangrenous area was sunken and there was a small zone of erythema around each one (Fig. 1). Over the back there was a series of similar lesions. There was considerable induration around the lesions. The dorsalis pedis arteries were palpable but the patient complained of numbness, tingling and tenderness over both feet. There was little evidence of peripheral vascular disease as far as the larger arteries were concerned. Cultures of the fluid in the blebs repeatedly showed a heavy growth of Staphylococcus aureus; probably due to secondary infection.

After the first 10 days, although new blebs continued to appear, an occasional one would be found on the legs and back. These ruptured and left the gangrenous ulcers described above. At the end of 4 weeks the ulcers began to improve, the change was characterized by thick, painless keratinous crusts which were followed by scaling and healing. The skin lesions were treated with dry heat in the form of baking continuously applied to

the exposed surface at a temperature as high as the patient could tolerate. No dressings, ointments or solutions were used. On December 23, when she left the hospital, the lesions on the back had scaled off leaving a purplish discoloration. The ulcers on the legs, although considerably smaller, were still present and covered by hard keratinous scales. (Fig. 2.) Although the lesions were painless she complained of cramp-like pains in the extremities.

Course in the Hospital. About 10 days after admission to the hospital she was awakened at 3 A.M. with a sharp pain in the left chest associated with cough, and expectoration of yellowish sputum. This was associated with generalized aching and a febrile rise to 103° F. There were no physical signs at first, later examination of the lungs revealed the presence of a slightly impaired percussion note with slightly harsh and high pitched breath sounds and numerous râles persisting after cough, over an area between the fourth and sixth dorsal spine just at the border of the left scapula. The amount of sputum increased, had a sweetish foul odor and varied from 4 to 6 ounces daily. Roentgenograms of the chest showed the

FIG. 2.—Three months later, showing healing and scaling with little scar formation.

presence of a mass in the region of the left hilus interpreted as lung abscess. She was placed on postural drainage and after 1 month roentgenograms showed definite healing. A roentgenogram taken March 2, showed complete healing of the abscess, and there has been no cough, expectoration or fever since then.

On admission the patient had a temperature of 102° F. The fever was intermittent in character with an afternoon rise to 102° and 103°, and a fall to normal during the night and morning. From October 22 to November 20, 1931, the temperature remained elevated and associated with this rise there were marked prostration and cramp-like pains in the extremities but no pain or tenderness over the ulcers. After November 9, the temperature fluctuated between 99.5° and 100° F. and each febrile rise was associated with the expectoration of large quantities of mucopurulent sputum. The sputum gradually diminished in amount and by December 23, she was raising less than 1 ounce daily. A total of 8 sputum examinations were negative for tubercle bacilli. Blood cultures and agglutination tests were reported negative. There was a slight anemia present, hemoglobin 10 gm.;

red blood cells 3,600,000; white blood cells 10,500 per c.mm. There was never any marked leukocytosis.

The diabetes was easily controlled. The diet on discharge contained 2500 calories, including 55 gm. of protein, 210 of fat and 100 of carbohydrate with 56 units of insulin daily.

By December 23, after 102 days in the hospital, the patient was discharged. Her condition was improved but she was far from cured. The lesions on the back had scaled off and left a purplish brownish pigmentation. She continued to use the hot bakes at home, weighed her diet carefully, and took 56 units of insulin daily. By January 3, the temperature came down to normal and remained there. She complained vigorously of cramp-like pains in the extremities, but not over the site of the lesions. On January 15 the pain was less and she tried walking. It was noticed that after lowering her feet a purplish discoloration developed at the site of the lesions. The legs were elevated for a few days and another attempt was made to exercise them, this time there was no discoloration and walking was encouraged, until she could walk about the house fairly well without much pain. She did, however, notice that on standing for any length of time a swelling would appear around both ankles. The cramp-like pains in the right leg entirely disappeared but she still complained of some prickling and darting pains in the left leg. Her general condition appeared good, the fasting blood sugar after her discharge from the hospital varied from 90 to 130 mg. per 100 cc. of blood.

Discussion.—Grangrenous lesions of the skin may be classified in three groups, (1) those due to circulatory disturbance, such as occur in Raynaud's disease and diabetes mellitus, (2) those that occur as trophic changes and, (3) those due to infections and caused by specific organisms. The last type mentioned is that which occasionally occurs in children with the acute exanthemata and is characterized by superficial necrosis. It is also found associated with certain acute inflammatory processes, usually abscesses in which drains have been placed.

The onset of dermatitis gangrenosa is marked by fever, perhaps a chill and prostration. The lesion may first be inflamed or first make its appearance as a large bleb surrounded by an area of edema. The subsequent ulcer extends down to the subcutaneous tissue, and when the overlying skin disappears granulations with shaggy fragments of slough are found. Bloodvessels are greatly dilated, filled with broken down pus cells and red cells. The margin of the gangrene is covered with a fibrinous exudate filled with neutrophils. The base of the ulcer is necrotic and covered with a seropurulent exudate. There is a narrow light red areola of hyperemia extending around the periphery. There may be lymphangitis and enlargement of the regional lymph nodes. Healing is characterized by the formation of a crust followed by scaling and healing.

There is no satisfactory explanation for the development of this form of dermatitis but careful studies have recently appeared concerning a bacterial etiology. Although no specific factor has been found, Brewer and Meleney[1] have been able to produce gangrenous ulcers by inoculation experiments in animals. In their investigation, the non-hemolytic streptococcus, the hemolytic staphylo-

coccus, and a diphtheroid organism were found. When the first two were inoculated separately in animals very little reaction occurred. When they were injected together gangrene was produced. From these results Brewer and Meleney[1] concluded "that a symbiotic function, or combination of functions of these two organisms may be necessary for the production of gangrenous ulcers." Besides this work numerous instances of such lesions have been reported in the literature. It is interesting to note that most of the cases have followed an appendectomy for appendiceal abscess. Cullen,[2] Brewer and Meleney,[1] and Shipley[3] report such cases. Lynn[4] reviewed the literature and reports 29 cases of postoperative gangrenous ulcer of the abdominal wall. Of these 15 occurred in males and 14 in females, and all followed appendicular abscess or peritonitis. However, Gatewood and Baldridge[5] and Meleney[6] have reported gangrenous ulcers following the injection of scarlet fever antitoxin. Warfield[7] reports a case in a patient with alcoholic neuritis and obesity. None of these ulcers have extended any deeper than the muscular aponeurosis and in no instance has there been any history of syphilis or diabetes mellitus.

Several explanations may be offered for the development of "dermatitis gangrenosa" in this case. One, a vascular disturbance of an obliterating type with lesions occurring at pressure points in a patient with a slow circulation and low blood pressure such as occurs in diabetic coma. The other explanations, also speculative, involve such factors as an extensive capillary bed, slow circulation, hyperglycemia, and bacterial invasion of the skin.

Treatment has been under discussion, and no agreement seems to have been reached. Probstein and Seelig[8] have used blood from immunized donors. Cullen,[2] Shipley,[3] Ballin[9] and Lynn[4] have been able to check the process and prepare the ulcer for skin grafting. Some have used quartz light and foreign protein shock. The fact that this has responded to such a gamut of therapy proves there is no accepted specific treatment. In our case treatment was directed toward the diabetes, and the extremities were kept warm.

Conclusion. A case of dermatitis gangrenosa is reported. Gangrene in diabetes is frequent especially where there are marked degenerative changes in the peripheral vascular systems. In such instances, however, gangrene is confined to the lower extremities. Superficial lesions are rare. An explanation for the development of the lesions is outlined.

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TEMPERATURE DETERMINATIONS IN THE FEMALE PELVIS DURING DIATHERMY.

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The markedly divergent opinions as to the therapeutic efficacy of diathermy in the treatment of pelvic inflammatory disease may be due to variations in the technique of its application. Obviously, the degree of temperature elevation and its duration bear a direct relationship to the therapeutic result obtained. Thus it is not surprising to note that Scheffey and Schmidt,[1] who produced temperatures between 101.5 to 102° F. as indicated by the thermometer in the vaginal electrode, did not obtain the same results as did Cherry[2] and others, who created temperature elevations between 108 and 110° F. as indicated by the vaginal electrode thermometer.

For the sake of accuracy the evaluation of therapeutic results should be related to the temperature elevations in the various parts of the female pelvis and the duration of these temperatures.

There is no method by means of which one may determine the degree of tissue heating which occurs during a pelvic diathermy treatment other than by direct thermal measurement. The reading of the milliamperemeter is no definite guide, because the heat produced by the passage of the high-frequency current varies with the extent of the area of tissue in contact with the electrode; the shape of the electrode; the character of the tissues traversed by the current; the integrity of the local circulation; the effectiveness of the thermoregulatory mechanism of the patient as well as the duration of current flow. The only way, therefore, to know the temperatures obtained during a treatment is by means of actual measurement. We have made such temperature determinations in order to guide us in the development of a technique which would produce the maximum amount of pelvic heating.

The heating effect of diathermy upon the structures of the female pelvis has been noted by several observers. These temperature determinations were made by means of a thermometer inserted into a vaginal electrode.[3] Because it was obvious that a thermometer so inserted measured the temperature of the metal composing

the electrode and not that of the tissues in contact with it, the channel containing the thermometer was extended to the surface so that the tip of the thermometer bulb was brought into contact with the vaginal mucosa.[2] In the effort to determine more accurately the temperatures developed in the treated tissues it was urged that thermometers be placed in the tissues and in no way incorporated into the electrode.[4] The temperatures registered by these thermometers rose to 110° F. and after a few minutes the temperature would drop 1 to 2°. To reëstablish an original temperature level it was necessary to increase the current.[5]

Observations have been made of the heat produced in the urinary bladder by means of diathermy. It has been shown that the rate of heating depends upon the concentration of the solution contained within the bladder.[6]

Diathermy produces an increased urinary secretion.[7, 8, 9] This increase has been explained as due to a dilatation of the bloodvessels of the kidney.

The application of diathermy to the pelvis causes an elevation of general body temperature.[3, 4, 10]

It has been shown that the use of "trans-pelvic diathermy" administered by means of plate electrodes placed externally (anterior posteriorly) does not cause any appreciable heating of the pelvic organs.[4, 6, 10, 16] On the other hand other observers have reported increases of rectal temperature as high as 3.6° F. by means of this technique.[17, 18]

Method. We have studied temperature changes produced by intrapelvic diathermy. The pulse rate, mouth temperature and the temperature of the voided urine were first determined. The patient was then placed upon the table and draped as for the usual gynecological treatment. A flexible metal belt, which we use as our dispersive electrode, was placed about her waist and connected to one terminal of the d'Arsonval winding of the diathermy machine. Thermometers were inserted as desired, into urethra, bladder, cervix or rectum for the measurement of the local temperatures during treatment. A lubricated vaginal electrode was inserted so that its concavity faced anteriorly and its upper end passed beneath the cervix into the posterior vaginal fornix. The vaginal electrode was connected with the other terminal of the d'Arsonval winding. This electrode (developed by Dr. Derow) is made in three sizes. The largest size compatible with the patient's comfort was used. A clamp support held the electrode and the thermometers in the various orifices.

We used clinical thermometers to measure the temperature of the urine directly after the patient had voided into a paper cup. We determined that the urinary temperatures obtained by this method were about one degree lower than their true values.

To determine the temperatures developed within the tissue of the cervix we employed a thermocouple made of chromel-copal wires inserted through capillary glass tubes placed within a hypodermic needle. With the coöperation of our physicist—Mr. Myron Schwartzchild—we made certain that the thermocouple readings accurately measured the temperatures of the treated tissues.[19]

Results. The readings of the vaginal electrode thermometer will here be designated as vaginal temperatures. If the strength of the diathermic current is rapidly increased, to reach the maximal milliamperage within 3 or 4 minutes, the vaginal temperature rises rapidly. When 2000 to 2500 ma. were applied in this manner, in the course of 34 treatments (Table 1), the maximal vaginal temperature, averaging 108.4° F., was usually reached in 10 minutes.

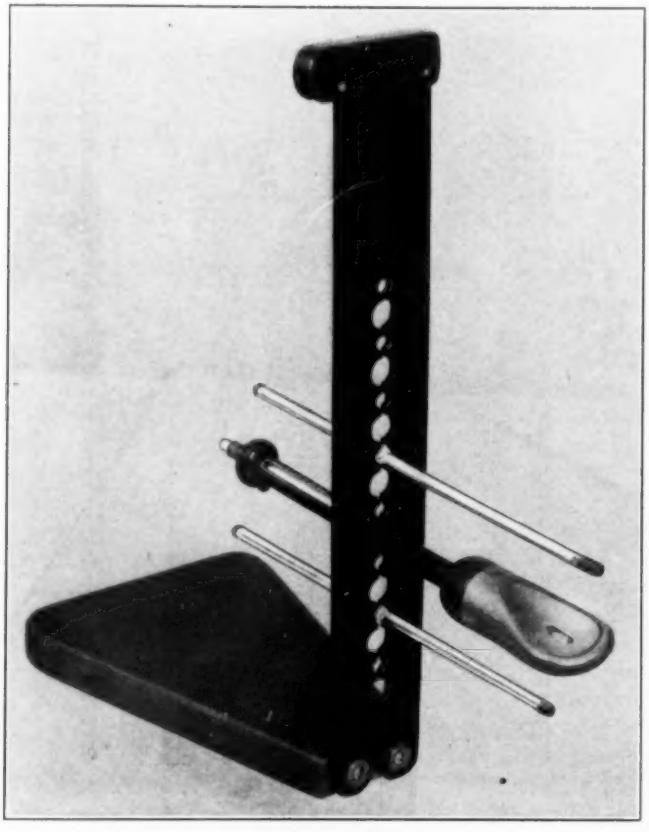

FIG. 1.—Clamp support for electrode and thermometers.

Although the milliamperage remained constant, a drop in temperature occurred averaging $2\frac{1}{2}$°, during the ensuing 15 minutes. This was followed by a very gradual, slight elevation amounting to about $\frac{1}{2}$ of 1° by the end of the 45-minute treatment.

If we increased the milliamperage gradually, at a rate of 200 ma. each minute, until the maximum of 2000 to 2500 ma. was attained, there was a more gradual and somewhat greater elevation of the

vaginal temperature. As shown in Table 2, during 21 treatments administered in this manner, the maximal vaginal temperature, averaging 109.8°, was reached in 16 minutes. This was followed by a drop of 3.3° during the succeeding 14 minutes. The vaginal temperature thereafter averaged but a ½° higher than during the treatments in which the current had been rapidly increased.

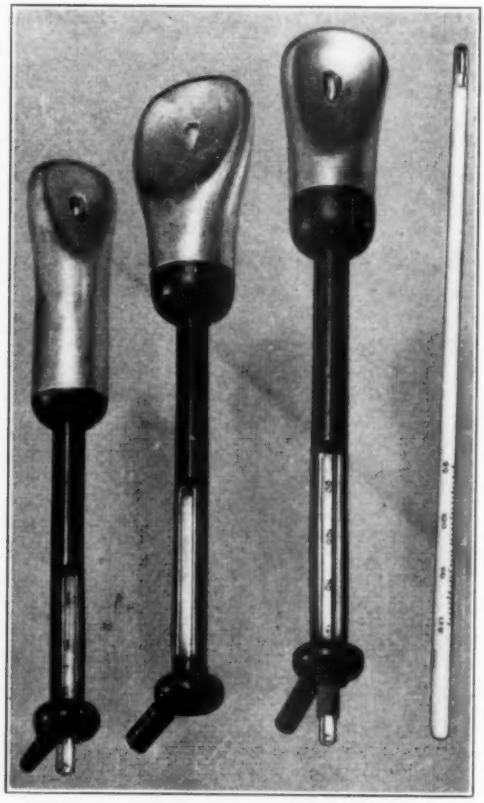

FIG. 2.—Derow vaginal electrode, three sizes.

The addition of more current just before the usual time of the drop in vaginal temperature, occasionally prevented and usually diminished this drop. After much experimentation, the best sustained vaginal temperature was found to be achieved by the following technique: Depending upon the bulk of the patient and the size of the vaginal electrode, the pelvic diathermy treatment was started with 1200 to 1500 ma. Ten minutes after the beginning of treatment, the current was increased another 500 ma., and this

was repeated 5 minutes later. Further increases were at 5-minute intervals, if necessary to maintain the temperature level. It was rarely necessary to exceed 3000 ma.

TABLE 1.—VAGINAL ELECTRODE TEMPERATURES DURING PELVIC DIATHERMY TREATMENTS.

	No. of treatments.	Maximal temp.	When reached, min.	Drop to:	When reached, min.	Temp. end of treatment.
2000 to 2500 ma. applied in first 3 min.	34	108.4	10	105.9	15	106.4
200 ma. every min. for 10 to 12 min. to 2000 or 2500 ma.	21	109.8	16	106.5	14	106.9
All cases recorded, various techniques	255	108.8	19	..	...	107.5

We have recorded the vaginal temperatures during 255 pelvic diathermy treatments administered to 40 patients. The average maximal temperature was 108.8° F. attained 19 minutes after the beginning of treatment. At the end of treatment, usually after about 45 minutes, the vaginal temperature averaged 107.5°. The highest vaginal temperature registered during any treatment was 112.5° F.

Throughout each treatment simultaneous observations were made every 5 minutes of the temperatures registered by the vaginal electrode thermometer, and by thermometers placed in one or more adjacent cavities.

Rectal Temperatures. Rectal temperatures were measured by means of a long mercury thermometer inserted a measured distance into the rectum, and held in place by the clamp support.

The highest rectal temperatures were recorded at a distance between 3 and 5 inches from the anal orifice (Table 2). Below 3 inches and above 5 inches the rectal temperatures were lower. With two thermometers registering simultaneously at varying distances within the rectum, temperature differences were similar to those shown in the table.

TABLE 2.—RECTAL TEMPERATURES AT VARYING DEPTHS DURING PELVIC DIATHERMY TREATMENT.

Penetration of thermometer, inches.	No. of treatments.	Maximal temp.	When reached, min.	Temperature end of treatment.
1½	5	105.0	39	104.9
2	10	106.3	32	105.8
2½	7	105.7	19	104.7
3	35	107.1	22	106.2
3½	17	107.3	21½	105.9
4	54	107.7	22	106.5
4½	3	108.7	27	106.7
5	7	107.1	15	106.1
6	3	103.9	25	103.9
Average rectal (all depths)	191	107.3	20	106.1
Average vaginal temperatures	255	108.8	19	107.5

In Table 2, it is seen that the average rectal temperature determined during 191 treatments, closely followed the average vaginal temperature, attaining its maximum at almost the same time, but remaining a degree and a half lower throughout.

Urethral and Bladder Temperatures. The temperatures registered within the bladder increased with the depth to which the thermometer was inserted. Three and 4 inches from the urethral meatus, the average maximal bladder temperatures were within a half degree of the average maximal vaginal temperatures, but were attained 6 to 13 minutes later. These deep bladder temperatures were better sustained than were the vaginal or rectal temperatures. At the end of treatment, the average bladder temperature had dropped but three-tenths of a degree from its maximum and was actually higher than the average terminal vaginal temperature.

The urethral temperatures averaged about 3 degrees lower than the deep bladder temperatures.

TABLE 3.—URETHRAL AND BLADDER TEMPERATURES DURING PELVIC DIATHERMY TREATMENTS. WITH THERMOMETER CONTINUOUSLY AT INDICATED DEPTHS FROM MEATUS.

Penetration of thermometer, inches.	No. of treatments.	Maximal temperature.	When reached, min.	Temperature end of treatment.
1	9	105.6	23	105.0
1½	98	105.8	26	105.3
2	20	106.5	29	106.2
3	12	108.2	32	107.9
4	4	108.7	25	108.4
Average vaginal temperatures	255	108.8	19	107.5

Urine Temperatures. Using the paper cup and clinical thermometer method previously described, the temperature of the urine before treatment averaged 98.4° F. on 271 occasions.

The temperature of the urine voided within a few minutes after the termination of treatment averaged 105° F. on 116 occasions. Since the determinations by this method proved to be about a degree lower than their true values, the temperature of these urines really averaged about 106° F.

In a few cases the urine was drained directly into a thermos bottle by means of a catheter, the catheter and thermos bottle having been previously heated to 100° F. Urine temperatures of 107° F. and over, were several times recorded by this technique.

Changes in Urine Concentration. Following about two-thirds of the treatments there occurred a diminution in the specific gravity of the urine varying between 0.002 and 0.014—averaging 0.005.

Mercury Thermometer Measurements of Cervical Canal Temperatures. Temperatures within the cervical canal were recorded simultaneously with the vaginal electrode temperatures during 8 pelvic diathermy treatments. We made certain by verifying its position at the termination of the treatment, that the entire bulb of the thermometer lay within the cervical canal. The cervical

temperatures closely followed the vaginal, averaging about 1 degree lower.

Thermocouple Measurement of Cervical Tissue Temperatures. In order to observe how the temperatures recorded by means of a thermocouple compared with the readings of a mercury thermometer, we inserted a thermocouple needle together with the bulb of a mercury thermometer into a cervical canal. The electrode was then introduced into the vagina, its end passing under the cervix without disturbing the cervical thermometers. The preliminary readings of the thermocouple and the thermometer in the cervix were almost identical (Table 4), while the vaginal electrode had not quite warmed up to body temperature. When the diathermy current was turned on, the thermocouple registered the elevation in temperature a little more rapidly than the cervical thermometer. Nineteen minutes from the beginning of the treatment the temperature recorded by the thermocouple, cervical thermometer and vaginal electrode thermometer simultaneously reached their peaks, with the thermocouple registering a temperature 0.9° F. higher than the mercury thermometer beside it. The subsequent drop in thermocouple temperature was also more rapid as was the further drop when the diathermy current was turned off. These differences are explained by the greater sensitiveness of the thermocouple. In this case the temperatures registered by the vaginal electrode thermometer were exceeded by the cervical canal temperatures.

TABLE 4.—THERMOCOUPLE AND MERCURY THERMOMETER SIDE BY SIDE IN CERVICAL CANAL.

Time.	Cervical temperature.		Vaginal electrode temperature.
	Thermocouple.	Mercury thermometer.	
3:17	98.5	98.6	96.6
3:18—2000 ma. on			
3:20	101.8	101.0	100.0
3:22	103.0	102.5	102.0
3:24	104.0	104.0	102.8
3:26	104.4	104.2	103.4
3:28	106.6	106.0	105.4
3:30	108.1	107.5	106.5
3:35	108.9	108.0	107.0
3:37	107.6	107.8	106.6
3:39	106.3	106.5	106.0
Machine off			
3:40	104.1	105.0	104.0
3:44	100.0	100.8	100.0

The thermocouple needle was inserted into the cervical tissue at different places. During the treatment, simultaneous observations were made at 2-minute intervals, by one worker with the thermocouple and by another reading the thermometers in the vaginal electrode and cervical canal. Thermocouple temperature usually was within 1 or $1\frac{1}{2}$° F. of the vaginal temperature.

In one instance we observed that the cervical tissue temperature rose to only 105° F. when the vaginal electrode thermometer read 109.5° F. In a few observations the temperature of the cervical tissue (as determined by thermocouple) was from 2 to 3° F. lower than that recorded by the vaginal thermometer.

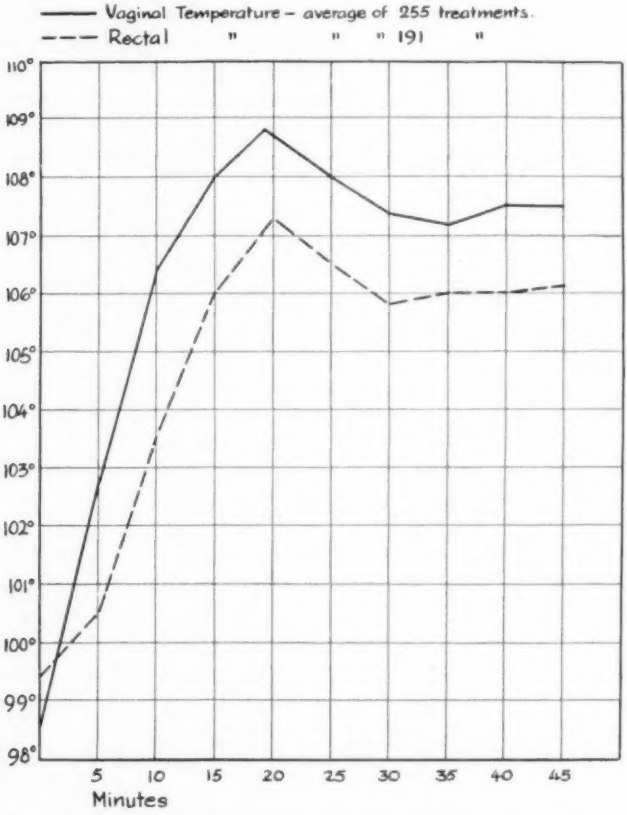

CHART I.—Average vaginal and rectal temperatures during diathermy.

Mouth Temperature Changes Following Pelvic Diathermy Treatments. An elevation of mouth temperature occurred following 215 (81%) of 264 pelvic diathermy treatments administered to 41 patients. This elevation varied between 0.1 and 2.4° F., the average being 0.7° F. A drop in mouth temperature followed 24 of the treatments. This drop varied between 0.2 and 1°, averaging 0.35°. Following the remaining 25 treatments, no change of mouth temperature was observed.

Pulse Changes Following Pelvic Diathermy Treatments. Of 267 treatments, 214 (80%) were followed by elevation of the pulse

rate, varying between 2 and 34 beats per minute and averaging 12 beats per minute.

In most instances the pulse elevation was accompanied by an elevation of mouth temperature. Occasionally the pulse was accelerated without a change of mouth temperature or even with a slight drop of mouth temperature. In a few cases there was an elevation of mouth temperature while the pulse was unchanged or had dropped a few beats per minute.

The Pelvic Heating by External Plate Electrodes. The highest internal temperatures which we have observed in any case during transpelvic diathermy, using large anterior and posterior plates, were: rectal 103.2° F., vaginal 102.2° F., bladder 101.9° F. The thermometers had been inserted at a depth of 3 inches into each of the orifices. A posterior plate 15 by 9 inches was used, and an anterior plate of 9 by 9½ inches. The treatment lasted 45 minutes and the maximal current was 2000 ma. The patient was uncomfortable during the latter part of the treatment because of excessive heating under the plates. An elevation of 1.2° F. in mouth temperature followed this treatment. During 8 other treatments with large anterior and posterior plate electrodes, the milliamperage averaged 1500 ma. The maximal rectal temperatures varied between 99.6 and 101°, the vaginal between 99.5 and 100.5°, the bladder between 99.8 and 100.5°. The cervical temperature never exceeded 99.9°. The temperatures mentioned were the maximal during the individual treatments. They were attained toward the end of treatment. The temperature of the urine voided after these treatments showed no appreciable elevation.

The region most heated by diathermy when applied with external plate electrodes appears to be the skin under the pubic margin of the abdominal plate. On one occasion a temperature of 109° F. was registered by a thermometer with its bulb under the abdominal plate at this point, 11 minutes after the beginning of treatment. 1500 ma. were used. The temperature under the electrode dropped during the ensuing 23 minutes and at the end of the 45-minute treatment was 105° F. It is interesting to observe that the temperature under the abdominal plate electrode when plotted on a chart shows the same characteristic drop as does the temperature curve obtained when using the active vaginal electrode technique.

Pelvic Diathermy with Rectal and Belt Electrodes. The pelvic organs may be effectively heated by diathermy when using a large rectal electrode in place of the vaginal electrode. The rectal electrode should have a large surface area so that a large amount of current may be applied without injury. A cylindrical electrode 4 inches long and ¾ to 1 inch in diameter, with a rounded end, is convenient for use in adults. For children we use a cylindrical rectal electrode 3 inches long. With the belt electrode about the waist and the large rectal electrode, 2000 to 2200 ma. are well

tolerated, and produce a temperature in the vagina of 106 to 108° F. After such treatment the bladder urine is likewise heated. We use the rectal electrode infrequently, chiefly for the treatment of virgins, because patients find its insertion somewhat disagreeable.

Discussion of Results. The average values reported are a reasonable true index of pelvic heating, but variations were encountered in individual cases. This is inevitable because the heating of the tissues by the current depends not only on the strength and duration of the current flow and the areas of application of the electrodes, but also upon the electrical resistance of the tissues. In addition there are variations due to differences in physiologic and pathologic conditions.

The vaginal electrode constructed of metal, is an excellent conductor of electricity and is not itself heated by the passage of the current. As it is also an excellent conductor of heat, it more or less rapidly assumes the temperature of the tissues with which it is in contact. When an electrode is equipped with a thermometer, the bulb of which is enclosed within it, the temperature recorded is the resultant of the temperatures of all points in contact with the electrode.

In the electrode which we used, the thermometer lies in a metal channel extending through the shaft into the active part of the electrode. About two-thirds of the surface of the thermometer bulb is in contact with the metal channel and the remainder is exposed for contact with the vaginal mucosa. For experimental purposes one of these electrodes was made with an additional channel for insertion of a second thermometer, inside the electrode. Simultaneous readings were made of the two thermometers, one entirely enclosed within the metal, the other partially in contact with the mucosa, throughout the diathermy treatment. It was found that the latter thermometer (the arrangement we use in practice) showed a slightly more rapid rise in temperature, was at first ½ to 1° higher and reached its maximum 4 or 5 minutes before the thermometer within the electrode. During the latter part of the treatment the two thermometers agreed fairly closely. We consider the thermometer in the vaginal electrode a valuable index of pelvic heating and a reliable guide during treatment.

By means of the paper cup-clinical thermometer method previously described, we measured the temperature of the urine before and after 35 Elliot treatments[30] administered at our clinic. The bladder temperatures attained during these treatments, as measured by a mercury thermometer introduced several inches beyond the urethral meatus, varied between 103 and 105.8° F. The urines voided after treatment, however, averaged but 99.4° F. The highest urine temperature was 101° F. Although the bladder wall had been heated through by conduction, the urine was evidently heated very little. During pelvic diathermy treatments the heating of the

bladder wall averaged but 2 or 3° higher than during the Elliot treatment, yet the temperatures of the bladder urine averaged 5½° higher. This could be explained by a direct heating of the urine itself, by the diathermy current.

The heating of the fluid in the bladder by the current and the well-sustained bladder temperatures suggest the likelihood that other fluid collections adjacent to the vagina, such as occur in the course of pelvic inflammation, may be heated similarly.

The relatively lower urethral temperatures reported by us, averaging almost 3° below the vaginal temperatures, demonstrate that the electrodes used were not adapted for maximal urethral heating. The electrodes were primarily intended for the treatment of pelvic inflammation and in a deep vagina, lay well above the urethra. Longer vaginal electrodes have recently been constructed.

Our intracervical temperature determinations were made by means of thermometers inserted within the cervical canal. We followed this procedure only in non-infected cases and under aseptic precautions. Otherwise, we would consider this procedure a potentially dangerous one. To quote Curtis, "There is distinct danger of low grade salpingitis from repeated instrumentation of the infected cervix."[21] We, therefore, do not consider it advisable routinely to insert a thermometer into the cervical canal and to keep it there throughout each pelvic diathermy treatment as suggested by Royston, Ewerhardt, Roblee and Zener.[4]

In considering the elevation of mouth temperature following 80% of our diathermy treatments, it should be remembered that the patients were draped with a sheet, just as for any other gynecologic treatment. No extra covering was used for the purpose of lessening heat dissipation. The fact that mouth temperature elevation did occur shows that heat was introduced into the bodies of these patients faster than they were able to dissipate it.

Conclusions. By means of a vaginal electrode equipped with a thermometer, the vaginal temperature was observed during 255 pelvic diathermy treatments.

A technique is described by means of which the vaginal tempera- may be maintained at a high level.

By means of mercury thermometers in cervix, bladder and rectum, the temperatures developed in these parts were found to follow closely the vaginal temperature, averaging but 1 or 1½° F. lower.

The use of a thermocouple needle demonstrated substantial heating of the tissue of the cervix.

The bladder urine was also heated to a high degree.

It has, therefore, been found that with the electrodes and milliamperages used, the reading of the thermometer in the vaginal electrode is a true indication of the temperatures attained in adjacent tissues.

Mouth temperature and pulse were elevated in 80% of the treatments.

The ineffectiveness of "trans-pelvic diathermy" by external plate electrodes as a method of pelvic heating was once more demonstrated.

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ACUTE PRIMARY DIAPHRAGMITIS (HEDBLOM'S SYNDROME).

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For some undetermined reason acute primary inflammation of the diaphragm went unrecognized and some neighboring organ received the blame for the trouble. Even in the works of Hippocrates[1] a mere mention is made of the anatomic aspects of the diaphragm. (Hippocrates' term "acute phrenitis," of course, refers to inflammation of the brain, not of the diaphragm.) We mention this point because of the recent popularization of such misnomers as phrenicoexairesis, or phrenicectomy, terms used for operations on the phrenic nerve which intend to paralyze the diaphragm in the treatment of pulmonary tuberculosis.

Obviously, the cacophonic term "acute diaphragmitis" is resorted to because the muscle is known by only one name. It would be

more euphonious as well as serviceable to refer to this entity as "Hedblom's syndrome" in honor of Dr. C. A. Hedblom who has devoted his life to thoracic surgery and died a few minutes after delivering one of his numerous presentations, all of which aided in placing the specialty of thoracic surgery on a popular footing.

This condition first attracted our attention in 1931, when we saw a patient with the following clinical picture:

Case Reports. Case 1.—Mr. P. D., a Greek fruit peddler, aged 38, was caught in the rain, October 11, 1931, and remained wet for 8 hours. By the time he reached home he developed a severe chill, a temperature of 103° F. and an abdominal pain. The pain was generalized at first, but later became localized in the right side of the abdomen. When seen by us, 2 hours after onset of the chill, the patient had painful breathing (ponopnea) and the only comfort he could have was in a sitting position. At this time the lungs showed no evidence of any involvement. There was a definite muscle spasm in the abdomen but generalized to the whole right side. The patient was sent to the Columbus Hospital, where a conservative régime was instituted in view of the absence of vomiting and leukocytosis. A basal pneumonia of the influenzal type was suspected. The patient was given inhalations of oxygen until his breathing became less labored and morphin until the pain subsided. He was kept in a semi-Fowler position because it gave the greatest comfort.

The next day the patient had a friction rub and subcrepitant râles in the right base. By October 14 the symptoms in the abdomen disappeared. He showed some tendency to cough but refrained because of pain it produced. On the next day the temperature came down to normal and remained there until he left the hospital, on October 16, 1931. When discharged he still complained of slight pain in the back of his chest on deep inspiration but the lungs showed no stethoscopic or other evidence of involvement. He was tagged with a diagnosis of influenzal pneumonia, but we were not satisfied with that classification because of the atypical picture of a pneumonia or appendicitis.

The exact etiology of the above syndrome revealed itself to us when we saw a patient who died following a perforated peptic ulcer. At autopsy he revealed a massive inflammation of the diaphragm with the formation of thick fibrinous exudate extending to the pleural side. An analysis of certain similarities of the symptom complex in the 2 cases lead us to assume that the diaphragm was really at fault in the first case. The following is a report of the second patient:

Case 2.—Mr. G. K., a German salesman, aged 47, enjoyed excellent health with the exception of a right inguinal hernia. No history of previous gastro-intestinal trouble. He developed the hernia 8 years ago by lifting a heavy suitcase. The company surgeon advised a truss which he wore for 8 years. Present illness started on April 3, 1932, with a severe stabbing pain in the abdomen which developed when he attempted to get up from bed. There was nausea but no vomiting, urinary retention or hematuria. When seen 30 minutes later, the patient was in agony. He presented a typical Hippocratic facies with sunken cheeks and eyeballs, beads of cold perspiration on his forehead and temples. The knees were drawn. Even the jarring of the bed aggravated the pain in the abdomen, which was rigid. Respirations were labored and painful. The pulse rate ranged

from 68 to 74 per minute. There was definite tenderness over the sac of a hernia which would not remain reduced because of the marked straining by the patient. The truss caused severe pain when applied and was therefore removed. The pain did not subside even with morphin, given in 2 doses of ¼ gr. each at an interval of 15 minutes. An examination of the chest showed no pulmonary or cardiac lesions to account for these symptoms. The patient was sent to the Columbus Hospital. There was no doubt that he presented an acute surgical condition of the abdomen, but was in shock, had a hernia which may have been strangulated and also presented signs of an upper right quadrant lesion that required surgical intervention. Of 3 surgeons who saw him, 2 decided against intervention, while the third insisted on a laparotomy, either in the upper abdomen or at the site of the hernia. A perforated ulcer was suspected but a Roentgen ray film revealed no pneumoperitoneum. On admission the white count was 6000 but on the following day it rose to 30,000. The severity of the condition was discussed with the wife, and the advisability of an exploration was discussed with her. As she refused operation, a watchful waiting régime was followed.

The pain in the abdomen persisted and was somewhat relieved by the use of opiates in large doses. The ponopnea persisted. There was no cough and no vomiting. The respirations were entirely costal in type, while the abdominal wall remained entirely rigid and immobile. A chest examination 24 hours after admission revealed mucous râles on both sides anteriorly and in the axillary areas. The facies of agony remained until the patient went into coma, about 5 hours before death, on April 6, 1932. About an hour before death there was persistent frothing from the mouth, indicating an acute edema of the lung.

At *autopsy* (Dr. Nora) the lungs showed acute edema, with no free pleural fluid. The diaphragmatic surface of the right lung as well as the pleural surface of the diaphragm showed a thick gray exudate with fibrinous adhesions between the lung and the diaphragm. The *heart* showed no important gross lesions. The *abdomen* contained some free seropurulent exudate. The serosal vessels of the whole bowel were injected. No gangrene was present. Above the hepatic flexure 500 cc. of thick grayish-yellow fluid were pocketed between the liver and the diaphragm. The peritoneal surface of the diaphragm showed a thick deposit of grayish-yellow bread-and-butter type of exudate. On further investigation a prepyloric perforated ulcer was located on the side of the lesser curvature. The perforation was the size of a dime; the area around it showed no induration. On section, the diaphragm was 3 times the thickness of its mate on the left side. The cecum and the site of the hernia showed no important lesions. There were no lesions in the pancreas, thus eliminating our suspicions of a possible hemorrhagic necrosis.

Analysis of this case reveals a silent prepyloric ulcer which on perforating caused a hyperacute diaphragmitis and local peritonitis as evidenced by the ponopnea and the board-like rigidity of the abdominal muscles. The ulcer may have been covered at a previous time by means of protective local peritoneal reaction. The ulcer undoubtedly perforated into this sac, thus preventing a generalized peritonitis. It is obvious why the patient did not have any vomiting since there was a relative absence of a generalized peritonitis. The diaphragm, therefore, received the greatest insult and consequently we noticed clinically an immobilization of the diaphragm as evidenced by costal breathing, ponopnea and painful cough.

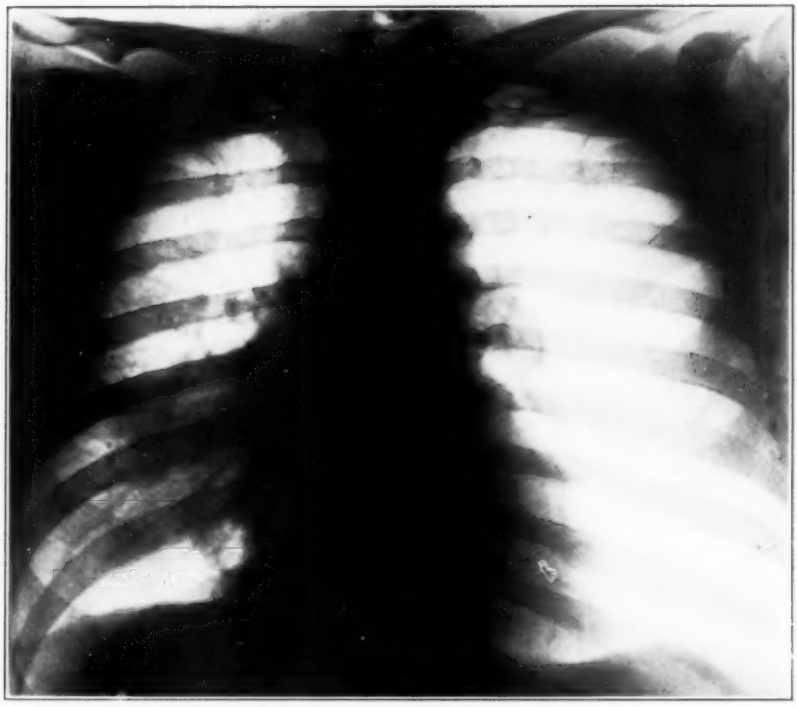

FIG. 1.—Case 3. Roentgenogram, taken on August 9, 1934, shows a definite rise of the right diaphragm. There is a slight obliteration of the normal dome of the diaphragm, and also a definite infiltration in the right hilum.

FIG. 2.—Case 3. Roentgenogram, taken on August 14, 1934, shows the hilar shadow cleared up. There is a rise of the diaphragm on the right side. The dome of the diaphragm is still evident.

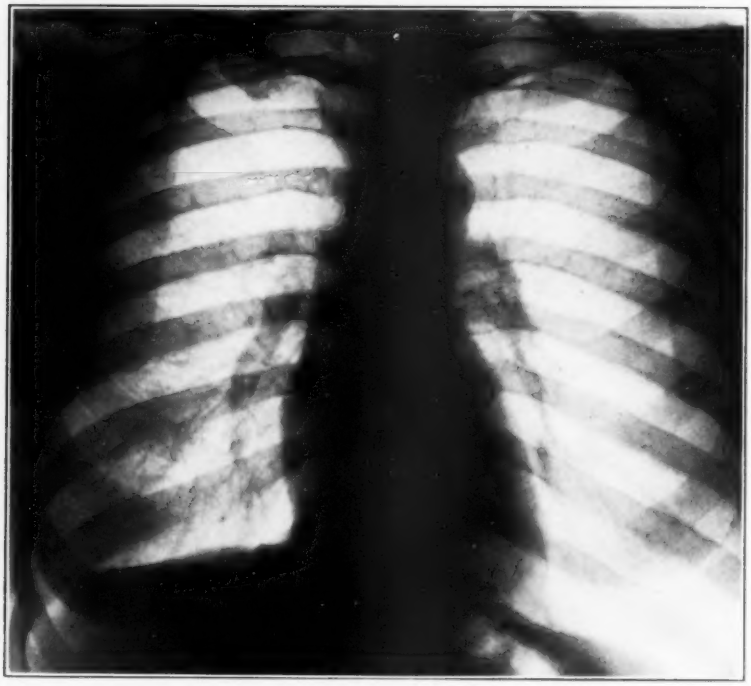

FIG. 3.—Case 3. Roentgenogram, taken on September 17, 1934. The pulmonary markings show no evidence of acute lesions. The dome of the diaphragm is almost entirely obliterated. The costophrenic angle is now about 90 degrees. There is a definite rise of the right hemidiaphragm.

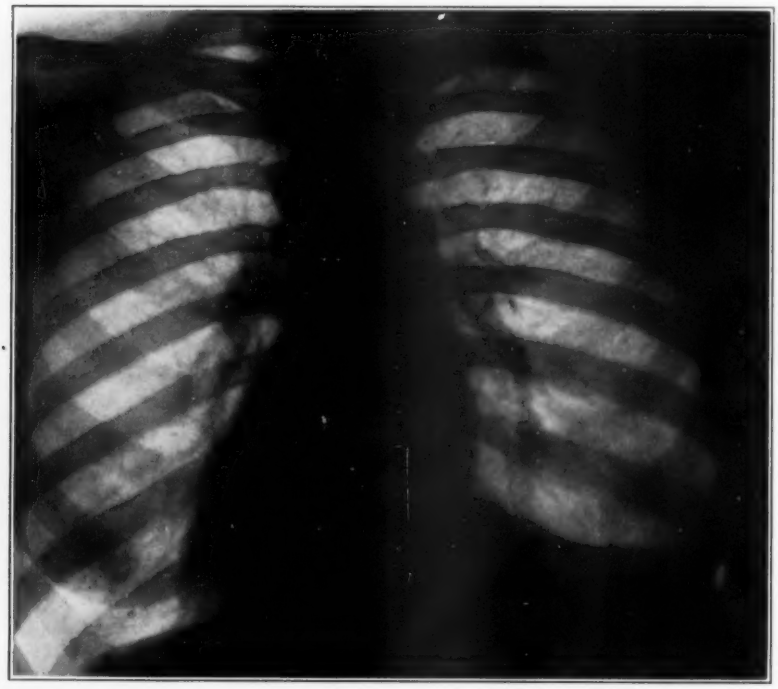

FIG. 4.—Case 3. Roentgenogram, taken on November 17, 1934. The Roentgen ray evidence of diaphragmatic rise and the obliteration of the dome is evident as in Fig. 3.

The similarity of this syndrome in the 2 patients as evidenced by abdominal pain, painful respiration and immobilization of the diaphragm lead us to suspect that the primary factor in the first case was an acute diaphragmitis. That such a syndrome is possible has been proven to our satisfaction by the third case, in which we have been able to demonstrate roentgenologically an immobilization of the diaphragm and the subsequent evidence of diaphragmatico-pulmonary adhesions.

Case 3.—Mrs. E. A., a Greek housewife, aged 40, presented herself on July 30, 1934, complaining of headache, nasal discharge and sore throat. On August 9, 1934, she called us to see her at the Garfield Park Hospital, because of pain in the region of the costal margin, at the angle of the scapula and the upper right quadrant of the abdomen. She placed herself under the care of a neighboring physician, (Dr. P. Hatzis), who made a diagnosis of right-sided pneumonia, based on the presence of râles in the chest. When seen by us, she still complained of the characteristic pain in the lower chest and upper abdomen but also had painful breathing. There was little or no cough. On the basis of our previous experience with the other 2 cases we arranged for a fluoroscopic examination which revealed an immobilization of the right leaf of the diaphragm. Roentgen films showed a slight rise of the right hemidiaphragm and a normal dome. There was also some evidence of parahilar infiltration of the lung which was diagnosed by Dr. Wait,* the roentgenologist, as pneumonia. She made an uneventful recovery. She was seen at our office on several occasions since her discharge from the hospital and a serial study of her diaphragm offers us a distinct proof that this patient suffered from Hedblom's syndrome. The Roentgen ray studies reveal a moderate rise of the diaphragm on the involved side. There is also a gradual obliteration of the normal dome of the hemidiaphragm no doubt due to one of two causes. Either fibrous tissue which may have been deposited is beginning to contract, or else costophrenic adhesions are pulling on the muscle and cause the gradual elimination of the normal dome.

Discussion. It may be considered bold of us to attempt the description of a new syndrome. We have hesitated for 2 years, until we felt certain of our ground. We believe that the serial Roentgen ray evidence is conclusive enough to encourage us to publish our observations.

There is no doubt that the syndrome is common and goes unnoticed because an associated picture masks the original entity. We believe that a lot of so-called pleurisies, particularly of the diaphragmatic type, are really those of Hedblom's syndrome. This may be also true of cases of so-called mild appendicitis, or cholecystitis. Certain basal pneumonias probably have their origin in an acute inflammation of the diaphragm.

The intimate relationship of the transversus abdominis with the diaphragm at their points of insertion[2] may explain the muscle spasm and rigidity of the abdominal muscles when the diaphragm is involved.

One may expect to encounter hiccough in such a syndrome.

* Through the kindness and permission of Dr. Wait the Roentgen pictures are reproduced for record and study.

This obviously is not to be expected, because hiccough in our experience is a phenomenon that involves the esophagus primarily and the pillars of the diaphragm secondarily. It is worthy of note at this point that the diaphragmatic pillars, although in some species an intimate part of the muscle, have a gastro-intestinal function.[3] Since in this syndrome the wing of the diaphragm is involved one may not expect hiccough.

Hedblom's syndrome evidently follows an acute nasopharyngeal inflammation much in the same manner as pneumonia, influenza, or even some cases of acute appendicitis. We are justified, therefore, in assuming that this syndrome is primary. Obviously, it may occur secondarily following lesions in the organs immediately above or below the diaphragm. When primary, it may be masked by more evident associated conditions. The presence of ponopnea should always lead us to suspect this syndrome.

Summary. 1. A hitherto undescribed syndrome is presented. It is hoped that it will be recognized as Hedblom's syndrome because it appears to be a distinct condition; the term is more suitable and phonetically more pleasing than acute diaphragmitis and because it honors this pioneer in thoracic surgery.

2. This syndrome is evidenced by painful breathing (ponopnea), painful coughing, an immobilization of the diaphragm as evidenced by the Roentgen ray and costal breathing. There is also abdominal pain involving generally the upper abdominal quadrant. Likewise there may be pain at the costal margin or even at the angle of the scapula.

3. Pathologically the diaphragm undergoes the changes of an acute exudative and proliferative inflammation. We believe that some of the muscle fibers are replaced by scar tissue and thus a flattening or even disappearance of the normal dome of the diaphragm results. The pleural surface may be involved by contiguity and cause diaphragmatico-pulmonary adhesions. The infectious agent causing the syndrome may extend by contiguity to the intrathoracic organs above or the intraäbdominal organs below.

4. This report is made in the hope that others will be on the lookout for the syndrome and particularly to avoid unnecessary operations on the abdominal viscera.

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VITAMIN A CONTENT OF HUMAN LIVER.

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The vitamin A content of 15 human livers obtained at autopsy, was determined.

Method. The total weight was noted. To each 100 grams of finely ground liver 500 cc. of 5% potassium hydroxid solution were added. After standing 48 hours this mixture was extracted 8 times with ether, and the extract washed 3 times with distilled water, or until the washings were not alkalin to litmus; the water removed by adding anhydrous sodium sulphate. It was then filtered and evaporated under vacuum to dryness. The residue was weighed as unsaponifiable matter. Spectrophotometric determinations on the non-saponifiable material were determined on Hilger's vitameter.

Table 1.—Vitamin A Content of Livers of 8 "Healthy" Persons.

Case	Age	Cause of death.	Total weight liver (gm.).	Non-saponifiable material in 100 gm.	Total No. I. U. of vitamin A in liver.	No. I. U. vitamin A per gram.	Remarks.
1	36	Pulmonary abscess (Vincent's)	2198	.237	129,682	59	Poor appetite; ill 3 months.
2	68	Heat prostration	2446	4.117	24,680	10	Diet: Low in vit.
3	73	Coronary thrombosis	1642	1.066	128,503	78	Diet: Unknown.
4	52	Accidental, fractured cerv. spine	1470	9.155	1,793,400	1220	Diet: Varied.
5	52	Coronary thrombosis	1860	1.415	169,427	91	Diet: Varied.
6	19	Accidental, ruptured stomach	2082	.539	294,187	141	Diet: Varied.
7	70	Coronary thrombosis	1792	.733	250,880	140	Diet: Unknown.
8	69	Cardiorenal vascular disease	1825	2.234	1,164,350	638	Diet: Unknown.
		Cases 1 to 8			Average	297	
		Cases 2 to 8			Average	331	

Results. In Table 1 are listed 8 cases which averaged 297 I. U. of vitamin A per gram of liver. All of these patients had a sudden lethal exodus except 1 (Case 1), who was ill with a pulmonary abscess (Vincent's) for 3 months. The 7, who were apparently healthy, averaged 331 I. U. of vitamin A per gram of liver. Case 2 lived on a houseboat and had a definitely low vitamin intake. Cases 4 and 6 were well nourished and well developed individuals. Both had

accidental deaths. Case 6 was known to have had a varied diet during his entire lifetime. Cases 4 and 8 evidently stored large quantities of vitamin A in the liver without the addition of any known quantity of vitamin A to their diets.

In Table 2 are listed 5 cases of tuberculosis, 3 of whom had been given additional vitamin A as halibut liver oil,* and 2 had had a high vitamin diet. Cases 9 to 12 averaged 523 I. U. of vitamin A per gram of liver. Case 13 is not included here because of the excessive administration of vitamin A—4,899,200 I. U. as halibut liver oil over a period of 142 days, 10 months before death. Loss of appetite was the cause for discontinuing the halibut liver oil. A total of 2,509,322 I. U. of vitamin A were found in the liver at death, or 3359 I. U. per gram.

TABLE 2.—VITAMIN A CONTENT OF LIVERS OF 5 CASES OF TUBERCULOSIS.

Case.	Age.	Dosage duration (days).	Total dosage H. L. O (gm.)	Total No. I. U. vitamin A adminis.	Cause of death.	Total weight liver (gm.).	Non-saponifiable material in 100 gm.	Total No. I. U. vitamin A in liver.	No. I.U. vitamin A liver per gram.	Remarks.
9	21	...	....	.....	Cerebral embolism and Tb. of hip joint	1291	.808	794,223	615	High vitamin diet
10	28	22	33.0	1,056,000	Pul. Tb., laryn. Tb. and intestinal Tb.	1426	1.905	543,306	381	Vit. A as H. L. O. High vitamin diet
11	18	12	18.0	576,000	Miliary Tb.	1070	.424	779,441	728	Vit. A. as H. L. O. High vitamin diet
12	30	...	....	.....	Miliary Tb.	1833	3.853	676,377	369	High vitamin diet
			Average						523	
13	57	142	153.1	4,899,200	Chr. Pul. Tb.	747	1.297	2,509,322	3359	Vit. A as H. L. O. High vitamin diet

In Table 3 are listed two children, who averaged 80 I. U. of vitamin A per gram of liver.

TABLE 3.—VITAMIN A CONTENT OF LIVERS OF 2 INFANTS.

Case.	Age.	Cause of death.	Total weight liver (gm.).	Non-saponifiable material in 100 gm.	Total No. I. U. of vitamin A in liver.	No. I. U. of vitamin A per gram.	Remarks.
14	2 yrs.	Miliary Tb.	500	2.244	47,715	95	Diet: Goat's milk.
15	1 mo.	Enlarged thymus	90	.642	5,796	64	Diet: Breast fed.
		Average				80	

* Purchased from Mead Johnson and Company, Evansville, Indiana.

Discussion. Wolff[1] and Moore[2] reported on the vitamin A content of human liver by using the antimony trichlorid method. Wolff's cases averaged 250 "Blue units" per gram. Moore reported that the average vitamin A reserve was 235 Blue units per gram. However, this method is not sufficiently accurate in quantitative determinations of vitamin A. The spectrophotometric method employed in this work has been approved by the International Conference on Vitamin Standardization.[3] In this series, 7 cases (Cases 2 to 8 inclusive) in apparently good health ranged from 10 to 1220 I. U. per gram, or an average of 331 I. U. of vitamin A per gram of liver.

Summary. 1. Spectrophotometric determinations of vitamin A content of human livers were performed in 15 cases.

2. Seven apparently healthy persons, dying sudden accidental deaths, averaged 331 I. U. of vitamin A per gram of liver. Two children averaged 80 I. U. of vitamin A per gram of liver. Four cases of pulmonary tuberculosis on a high vitamin diet averaged 523 I. U. of vitamin A per gram of liver.

3. The addition of vitamin A as halibut liver oil stores a large quantity of vitamin A in the human liver.

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BOOK REVIEWS AND NOTICES

THE ADVANCE OF SCIENCE. Edited by WATSON DAVIS, Director, Science Service, Washington. Pp. 400; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1934. Price, $3.50.

THIS popularizing assemblage by the Director of Science Service (21 of the 32 chapters are apparently written by others) aims "to outline the extent to which that knowledge (*i. e.*, of man and Nature) has now advanced in each of the major fields of scientific endeavor." Astronomy, physics, chemistry, geography, transportation, medicine, archeology, each is treated in a "march-of-time" manner, that offers many targets for the critic, both of selection of topic and of statements made. Yet, like its prototype, Science News Service, the book contains accounts of so many recent developments that there are few, indeed, even among scientists, who will fail to find much that is new and interesting. E. K.

BODY MECHANICS. In the Study and Treatment of Disease. By JOEL E. GOLDTHWAIT, M.D., LL.D., Member of Board of Consultants, Massachusetts General Hospital, etc., LLOYD T. BROWN, M.D., Instructor, Orthopedic Surgery, Harvard Medical School, LORING T. SWAIM, M.D., Instructor, Orthopedic Surgery, Harvard Medical School, and JOHN G. KUHNS, M.D., Assistant in Orthopedic Surgery, Harvard Medical School. Pp. 281; 99 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, $4.00.

HERE are summarized in book form the teachings of Dr. Goldthwait. For many years the Boston group of orthopedic surgeons, under the leadership of Dr. Goldthwait, have dwelled at great length upon the value to all persons of the correction of faulty body mechanics. To the chronic invalid, regardless of the cause of his invalidism, they have held out the benefits which would result from the overcoming of defects in posture. That benefits would result is well known to the American orthopedists. Such knowledge is not had by the general practitioner. To him this book should be of great value in explaining "why" and telling "how."

G. W.

BIOLOGY FOR MEDICAL STUDENTS. By C. C. HENTSCHEL, M.Sc. (LOND.), Lecturer in Zoölogy, Chelsea Polytechnic, etc., and W. R. IVIMEY COOK, B.Sc., PH.D. (LOND.), Lecturer in Botany, The University, Bristol, etc. With a Foreword by G. E. GASK, C.M.G., D.S.O., F.R.C.S., Professor of Surgery and Dean of the Faculty of Medicine in the University of London, etc. Pp. 618; 413 illustrations. New York: Longmans, Green & Co., 1932. Price, $7.00.

"THIS book is primarily intended for the use of medical students in their first year in biology. It covers the syllabuses for the First M. B. Examination of the University of London, and also for the Pre-medical Examination for the Conjoint Examining Board in England of the Royal Colleges of Physicians and Surgeons. A notable feature is that both the Botanical and Zoölogical aspects of the subject are included in one volume." (Publisher's note.)

ELEMENTARY HUMAN ANATOMY. Based on Laboratory Studies. By KATHARINE SIBLEY, Professor of Physical Education, School of Education, Syracuse University. Pp. 360; 213 illustrations, many in colors. New York: A. S. Barnes & Co., Inc., 1935. Price, $4.50.

"THIS text for an undergraduate [Dept. of Physical Education] course in human anatomy is written as a foundation for the study of kinesiology and physiology. The author has placed special emphasis on osteology, syndesmology, myology and the nervous system to aid the teacher of corrective physical education and physiotherapy in muscle examination and muscle reëducation. Each chapter is accompanied by laboratory studies and these studies are based on live muscles wherever possible." (Publisher's note.)

THE CRIPPLED AND THE DISABLED. Rehabilitation of the Physically Handicapped in the United States. By HENRY H. KESSLER. Pp. 337. NEW YORK: Columbia University Press, 1933. Price, $4.00.

"Coming as it does in the midst of the largest national project for normal economic and social adjustment, . . . [this] book on the needs of the crippled and disabled should turn the attention of the socially minded to this unique problem.

"The popular fallacy that all disabled persons constitute a unit of sheer economic waste is quickly and totally dispelled. Physical limitations they may have, but the handicapped can be rehabilitated so as to become useful, self-supporting and responsible members of the community. Rehabilitation is, therefore, the key to the problem. Efforts for the reëducation of the community at large toward this unfortunate group must be met by legislative measures. A plea is made for more adequate and uniform legislation, so that all types of handicapped may be received by authorized state or federal agencies set up to adjust these individuals to the types of occupations peculiar to their specific disability.

"A detailed study is made of disabled persons classified according to type; this, together with perhaps the most comprehensive critical evaluation of the laws pertaining to this subject, comprise the basis of a book dealing with a vital problem." (Publisher's note.)

THE PHYSICAL AND MENTAL GROWTH OF PREMATURELY BORN CHILDREN. By JULIUS H. HESS, M.D., Professor of Pediatrics, College of Medicine, University of Illinois; Attending Pediatrician, Illinois Research, Cook County and Michael Reese Hospitals, GEORGE J. MOHR, M.D., Director, Pittsburgh Child Guidance Center, etc., and PHYLLIS F. BARTELME, PH.D., Psychologist, Cook County Juvenile Court, Chicago; Research Psychologist, Institute for Juvenile Research. Pp. 449; 90 illustrations and 161 tables. Chicago: University of Chicago Press, 1934. Price, $5.00.

PROGNOSIS is such an important aspect of clinical medicine that a monograph which furnishes reliable data is always welcome. Such a monograph is this by Dr. Hess and his associates. The Premature Infant Station of the Sarah Morris Hospital is well known to American pediatricians and they will find in this volume an immense amount of valuable material concerned with the immediate and remote prognosis of the infant prematurely born.

The book has been divided into three parts, but might just as well have been divided into two; the clinical studies by Dr. Hess on the immediate morbidity and mortality, together with the development and growth studies by Drs. Mohr and Bartelme, and the collection of previously pub-

lished papers by other associates. Indeed there is some doubt in the Reviewer's mind as to the propriety of including this latter material at all.

Dr. Hess' study of immediate mortality and morbidity and the etiology of prematurity is complete. Ample protocols of the necropsies of all fatal cases are available. Dr. Hess is to be congratulated that his results in the case of these babies become increasingly favorable.

A second division of the volume concerns itself with a statistical analysis of the fate, growth and development of the "graduates" of this Station. A wealth of material based upon careful studies of 250 children is presented from every aspect concerned with prognosis. The conclusions point out that early care and constant supervision have much to do with the results which seem more optimistic than those presented by other writers, such as Capper, Steinfuth and Yepps.

Any reader seeking for information about the care of immature children will be disappointed with this book. Only two of the appended special articles deal with phases of that subject—anemia and the use of oxygen therapy. For those seeking information upon which to base prognosis this volume can answer any question. E. T., Jr.

Human Anatomy. Double Dissection Method. By Dudley J. Morton, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. (First Dissection) 265, illustrated. Pp. (Second Dissection) 554, illustrated. New York: Columbia University Press, 1934. Price, $3.00 each.

"The time allowed for anatomy [in medical school curricula] has been very much reduced. Faced with this fact, a choice between two alternatives has inevitably been imposed; either to contract the former plan of teaching into half the time previously allowed—a method which places the students at a distinct disadvantage, or to create new methods to meet new conditions. The latter alternative is represented in the Double Dissection plan developed in the College of Physicians and Surgeons, New York. . . . The unusual features of the course form a 1-year course in anatomy of about 360 hours, which carries the students through two dissections of the entire body *with no greater expenditure of anatomical material than is ordinarily used.* The first dissection applies only to the larger structures, and gives students a preliminary understanding of those structures as a basis for the subsequent detailed dissection. The plan is designed for utmost economy in time and effort, with maximum pedagogic results." (Publisher's note.)

The Clinical Aspects of Visceral Neurology. With Special Reference to the Surgery of the Sympathetic Nervous System. By W. K. Livingston, M.D., Clinical Associate in Surgery, University of Oregon Medical School. Pp. 254; 46 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

The structure of the nervous system is much better known than are its functions. The author summarizes present-day knowledge by stating: "The function of the visceral nervous system is to regulate visceral activity so that the organism is brought into harmony with the ever-changing internal and external environment." It is this system which is intimately concerned with the maintenance of the "steady states" (to use Professor Cannon's happy phrase) which are characteristic of the higher forms of living creatures. There are a number of texts that deal with the visceral nervous system (the "vegetative," "involuntary," "autonomic," "sym-

pathetic and parasympathetic" system) from the standpoint of the experimental investigator; the present monograph deals primarily with clinical aspects. The first part of the book (pp. 5 to 58) is a summary of the anatomy and physiology; of particular interest to clinicians is the chapter on normal regulation of bloodvessel function and a discussion of visceral pains. The second part (pp. 59 to 130) deals with conditions that have been treated by visceral nerve surgery: functional disturbances and organic diseases of the arteries (such as Raynaud's disease, hypertension, thromboangiitis obliterans; angina pectoris), chronic arthritis and certain pelvic disorders. The third part of the monograph (pp. 131 to 226) is devoted to surgical procedure and general discussion. There are chapters on prognostic methods, surgical technique, surgical treatment of intractable pain, etc. The viewpoint of the author is expressed in the following quotation from the introduction: "It would be a mistake to consider sympathetic nerve surgery a panacea. On the contrary, cutting sympathetic pathways does not, as Sir Thomas Lewis has often reiterated, effect 'cures' in the sense that the underlying cause has been removed. The procedure might well be likened to the cutting off of lines of communication of an invading army. The fact that the communications have been severed does not destroy the army, but does handicap its advance, and may prove the means by which the tide of battle turns in favor of the defending forces." B. L.

THE MEDICAL CLINICS OF NORTH AMERICA. VOLUME 18, NO. 3 (NEW YORK NUMBER—NOVEMBER, 1934). Pp. 301; 17 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, per clinic year, July, 1934 to May, 1935, paper, $12.00; cloth, $16.00.

"A RADICAL change in policy is inaugurated with the publication of this number. Hereafter the *Medical Clinics* will feature the everyday 'run-of-practice' problems of the general practitioner. Emphasis will be placed upon diagnosis and treatment. The symposium idea will be further developed so that, insofar as possible, each number will contain a group of clinics dealing with the various clinical phases of some important diagnostic or therapeutic problem. Among the symposiums to be published during 1935 will be: 'The Treatment of Heart Disease,' 'Allergic Diseases,' 'The Medical Management of Biliary Disease,' 'The Treatment of Pneumonia.'

"These new *Medical Clinics* will present in detail certain definite clinical aspects of a condition, rather than general discussions. In other words, the *Clinics* will give the reader the clinical meat of a problem such as he would expect to obtain while in actual attendance at a postgraduate clinic." (From Publishers' Notice.)

COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, VOLUME 2. Pp. 284; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1934. Price, $3.35.

THE second volume of these symposia is chiefly concerned with various aspects of growth. Of the 34 articles presented only a few are by the authors included in Volume 1, though familiar names appear among those taking part in the discussion. A number of the presentations are on the chemistry of growth, genic factors and yeast; protozoa and amphibia as material for growth study. The necessary physical and mathematical backgrounds are also represented in some half dozen articles. We can only repeat our high praise of this effort to bring together in a novel way authorities in different fields of science in order to promote a discussion of biology that is as far as possible quantitative. E. K.

AN ATLAS OF THE COMMONER SKIN DISEASES. By HENRY C. G. SEMON, M.A., M.D. (OXON.), M.R.C.P., London, Physician for Diseases of the Skin, Royal Northern Hospital. Photography under the direction of ARNOLD MORITZ, B.A., M.B., B.C. (CANTAB.). Pp. 221; 103 colored plates. Baltimore: William Wood & Co., 1934. Price, $12.00.

BY a fortunate combination of the Finlay color photography method with the products of highly skilled engravers, this *Atlas* offers the best photographs in natural color of living subjects that the Reviewer has ever seen. Opposite each plate, abbreviated clinical descriptions and notes on differential diagnosis and treatment are given as *aides memoires*. In addition to the commoner skin diseases, 13 of the rarer forms are included. As far as the eye can contribute, these plates are as good as seeing the patient himself. E. K.

THE JEW IN SCIENCE. By LOUIS GERSHENFELD. Pp. 224, Philadelphia: The Jewish Publication Society of America, 1934. Price, $2.75.

THE present vogue for colorful biography, accentuated by the world's concern in a great nation's drive to rid itself of one of its most useful groups of citizens, arouses one's interest as soon as this title is read. The author, who "has interested himself for years in the history of science, Judaism and scientists," has not only given the high lights of a dramatic story of racial history in the first half of the book, but has furnished a useful reference work in the second half on modern Jewish scientists in medicine and other fields. As a reference book, it would be much more useful if the groups had not been rather arbitrarily and unsystematically subdivided or if an adequate index had been provided. E. K.

ONE HUNDRED AND FIFTY YEARS OF PUBLISHING, 1785–1935. [HENRY CHARLES LEA.] Pp. 42; illustrated. Philadelphia: Lea & Febiger, 1935.

THOSE who have a penchant for long-lived institutions, and even believe that long life may contribute to their present efficiency, will be especially pleased with this record of one of the oldest publishing houses in the country. It is also one of the oldest firms in a city that has the largest number of firms in America that have been in continuous existence for over a century. Philadelphia can well afford to accept without rancor, even with pride, the chaffing that it may get from less stable sisters on such matters. Amplified from the sketch prepared by Henry C. Lea 50 years ago, our anniversary book describes the firm's activities and changes during 150 years. Especially picturesque is the account of its founder, Matthew Carey, an Irishman who came to this country in 1784, was "staked" in business by his friend, Lafayette (repaying the benefaction some 40 years later), wrote against duelling and later was wounded in a duel, brought his publishing firm into a leading position in this country, and founded (1820) *this Journal*, the oldest medical monthly in the country, and one of the very oldest medical periodicals in the English language. This journal (whose 11 editors are listed), the American edition of Gray's Anatomy (published since 1859) and Osler's "Modern Medicine" can perhaps be singled out from many successes as the firm's most important contributions to medicine. Of the 14 names that the firm has held, that of Henry C. Lea (1865–1880), one of America's greatest historians, is perhaps the most celebrated. The present senior member is fifth in direct descent from Matthew Carey. Long may the firm flourish in its business of furnishing "Quae prosunt omnibus."

E. K.

NEW BOOKS.

Diseases of the Mouth and Their Treatment. A Textbook for Practitioners and Students of Medicine and Dentistry. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc., Dr. Med. Dent., Professor of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania, and SIGMUND S. GREENBAUM, B.S., M.D., Associate Professor of Dermatology and Syphilology in the Graduate School of Medicine of the University of Pennsylvania; Attending Dermatologist, Mt. Sinai and Philadelphia General Hospitals. Pp. 602; 287 illustrations and 11 colored plates. Philadelphia: Lea & Febiger, 1935. Price, $9.00.

Biology for Medical Students. By C. C. HENTSCHEL, M.Sc. (LOND.), Lecturer in Zoölogy, Chelsea Polytechnic, etc., and W. R. IVIMEY COOK, B.Sc., PH.D. (LOND.), Lecturer in Botany, The University, Bristol, etc. With a Foreword by G. E. GASK, C.M.G., D.S.O., F.R.C.S., Professor of Surgery and Dean of the Faculty of Medicine in the University of London, etc. Pp. 618; 413 illustrations. New York: Longmans, Green & Co., 1932. Price, $7.00. (Review, p. 574.)

Elementary Human Anatomy. Based on Laboratory Studies. By KATHARINE SIBLEY, Professor of Physical Education, School of Education, Syracuse University. Pp. 360; 213 illustrations, many in colors. New York: A. S. Barnes & Co., Inc., 1935. Price, $4.50. (Review, p. 575.)

Human Anatomy. Double Dissection Method. By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. (First Dissection), 265, illustrated. Pp. (Second Dissection) 554, illustrated. New York: Columbia University Press, 1934. Price, $3.00, each. (Review, p. 576.)

Practical Neurological Diagnosis. With Special Reference to the Problems of Neurosurgery. By R. GLEN SPURLING, M.D., Assistant Clinical Professor of Surgery (in charge of neurosurgery), University of Louisville School of Medicine. Pp. 233; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

The Jew in Science. By LOUIS GERSHENFELD. Pp. 224. Philadelphia: The Jewish Publication Society of America, 1934. Price, $2.75. (Review, p. 578.)

The Crippled and the Disabled. Rehabilitation of the Physically Handicapped in the United States. By HENRY H. KESSLER. Pp. 337. New York: Columbia University Press, 1935. Price, $4.00. (Review, p. 575.)

French Medicine. Volume 15 of Clio Medica. By M. LAIGNEL-LAVASTINE, Professor in the Medical Faculty in Paris; Secretary General of the International Society of Medical History, and M. RAYMOND MOLINERY, Gold Medalist of the Academy of Medicine; Member of the French Society of Medical History. Translated by E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania. Pp. 187; 14 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $2.50.

Mouth Infection. Clinical Histories. By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., Professor of Therapeutics, Emeritus, and formerly Clinical Professor of Medicine, Yale University. Pp. 119. New Haven: By the author, 1934. Price, $2.00.

A short summary with subject matter classified under three heads: (1) Teeth and gums; (2) tonsil infection; (3) Vincent infection, tongue, adenoid growths and the toothbrush. F. W.

The 1934 Year Book of Obstetrics and Gynecology. Obstetrics. Edited by JOSEPH B. DELEE, A.M., M.D., Professor of Obstetrics, University of Chicago Medical School; Chief of Obstetrics, Chicago Lying-In Hospital and Dispensary in affiliation with the University of Chicago. *Gynecology.* Edited by J. P. GREENHILL, B.S., M.D., F.A.C.S., Associate Professor of Gynecology, Loyola University Medical School; Professor of Gynecology, Cook County Graduate School of Medicine, etc. Pp. 717; 96 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, $2.50.

The 1934 Year Book of Pediatrics. Edited by ISAAC A. ABT, D.Sc., M.D., Professor of Pediatrics, Northwestern University Medical School; Attending Physician, Passavant Hospital, etc. With the collaboration of ARTHUR F. ABT, B.S., M.D., Associate in Pediatrics, Northwestern University Medical School; Adjunct Attending Pediatrician, Michael Reese Hospital, etc. Pp. 541; 74 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, $2.25.

Rats, Lice and History. Being a Study in Biography, Which After Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals With the Life History of Typhus Fever. By HANS ZINSSER. Pp. 301. Boston: Little, Brown & Co., 1935. Price, $2.75.

The Care of the Aged, the Dying and the Dead. By ALFRED WORCESTER, M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 77. Springfield, Ill.: Charles C Thomas, 1935. Price, $1.00.

Fracastor. Syphilis or the French Disease. A Poem in Latin Hexameters. By GIROLAMO FRACASTORO. With a Translation, Notes and Appendix by HENEAGE WYNNE-FINCH, M.A. (OXON.), and an Introduction by JAMES JOHNSTON ABRAHAM, C.B.E., D.S.O., M.A., M.D. (DUB.), F.R.C.S. Pp. 253; illustrated. London: William Heinemann, Ltd., 1935. Price, 10/6.

Surgical Diseases of the Chest. By EVARTS AMBROSE GRAHAM, A.B., M.D., F.A.C.S., Professor of Surgery, Washington University School of Medicine, St. Louis; Surgeon-in-Chief, Barnes and St. Louis Children's Hospitals, etc., JACOB JESSE SINGER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician, Barnes Hospital, etc., and HARRY C. BALLON, M.D., C.M., F.A.C.S., formerly Assistant Professor of Surgery, Washington University School of Medicine; formerly Assistant Surgeon, Barnes Hospital. Pp. 1070; 637 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $15.00.

NEW EDITIONS.

Dietetics for the Clinician. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Department of Correction Hospitals, New York, etc. Foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University, New York. Pp. 970; 64 tables. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $10.00.

The first edition of this work was described by the Reviewer as deserving emphatic recommendation. His judgment has been confirmed by the popularity of the work which has led to a second edition within less than 2 years. The new volume, greatly amplified and in part rewritten, is an improvement on the first. R. K.

Allergische Diathese und Allergische Erkrankungen. By DR. HUGO KÄMMERER, Professor der Universität München, Leitendem Arzt der Inneren Abteilung des Nymphenburger Krankenhauses zu München. Pp. 359; 4 illustrations. Second edition, enlarged and improved. München: J. F. Bergmann, 1934. Price, paper, Rm. 26; bound, Rm. 29.60.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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OVARIAN TUMORS.

PROBABLY the most common complication of all ovarian tumors is torsion or twisting of the tumor on its pedicle, and while many theories have been advanced as to the cause of this phenomenon, it still remains in the field of speculation. Shaw[1] states it to be a well-established clinical fact that a history of exertion or violent movement is frequently obtained in cases of torsion. It is suggested that these movements result in a rotation of the tumor through half a circle or more. In cases which arise independently of such movements, similar small twists may be induced through movements of the sigmoid or rotations of the body of the patient, such as turning over in bed. He suggests that the next factor in the production of torsion is hemodynamic. However slight the torsion of the ovarian tumor, the ovarian artery must be both stretched and twisted. Most important of all, the twist of the artery is in the same direction as the original twist of the cyst. The twisted artery pulsates, for in the original stage of torsion the lumen of the vessel is not obliterated. With each pulsation a column of blood, the dimensions of which are determined by the lumen of the artery, is forced through the artery. As the wall of the vessel is twisted, part of the momentum of the blood is spent against the wall and the force exerted will always be in the direction of the twist. In other words, the pedicle of the cyst is subjected to a series of small impulses, each of which tends to increase the extent of the twist. Though each impulse is extremely small, the combined effect of the impulses in rotating the tumor, recurring 72 times per minute, will be considerable. The tumor itself is free to move and pain develops when the veins become occluded and the tumor becomes engorged with blood. On this theory further torsion will cease as soon as the main artery in the pedicle is occluded. It should be remembered that torsion is often spontaneously reduced, which is rather difficult to explain under the above theory, although, of course, it is doubtful if

cases in which there are extreme degrees of torsion ever reduce themselves spontaneously.

Carcinoma. In a group of 403 cases of adenocarcinoma of the ovary in which operation was performed at the Mayo Clinic, Moench[2] states that 254 were papillary cystadenomas, 72 carcinomatous cystadenomas and 77 solid adenocarcinomas. The incidence of adenocarcinoma of the ovary is highest in the fifth and sixth decades of life. There are no characteristic symptoms of this disease. Abnormality of ovarian function was apparent through disturbance of menstruation evidenced by recent change in periodicity, profuse flow, scanty flow or metrorrhagia. Pain was an outstanding symptom in over half of the cases. Three years after operation nearly 60% of the patients were living, the best results being obtained in those patients who had papillary cystadenoma. In a fourth of the patients the tumor was bilateral and in these the length of life after operation was shorter and only half as many survived the 3-year period as when the tumor was unilateral. Intracystic malignancy was less likely to recur than extracystic malignancy. Of the patients who had metastases, 30% were living 3 or more years later, the results being better in those who had only pelvic metastases compared to those who had both pelvic and abdominal involvement.

In a study of the incidence of malignancy of the ovary in the first 3 decades of life, Schreiner and Wehr[3] found that of 2405 gynecologic malignancies admitted to the State Institute for the Study of Malignant Disease at Buffalo, 114 (4.6%) occurred during this period, and of these, malignancy of the ovary represented 10.6% (23 cases). Of these, 6 were papillary cystadenocarcinomata, 6 adenocarcinomata, 9 carcinomata, 1 sarcoma and 1 malignant teratoma. Two of the cases were between 10 and 15 years of age, 3 between 16 and 20, 8 between 21 and 25 and 10 between 26 and 30. Of the 23 patients, 13 were unmarried, while 2 of the married patients had no pregnancies. These figures should remind us that the so-called carcinoma age may begin early in life rather than at 40 as so often inferred.

Granulosa Cell Tumors. The gynecologic literature for the past few years is fairly teeming with discussions about ovarian tumors which are associated with changes in the secondary sexual characteristics. While these tumors are not common, they are apparently more frequent than was formerly believed and have been found by several pathologists in checking back on old slides in which they were originally missed. In discussing granulosa cell tumors Novak and Long[4] state that it is commonly believed that they arise from the early oöphorogenic structures in the sex gland area. The evidence seems to point to the fact that the real germinal epithelium of the ovary is derived from the mesenchyme of the sex gland anlage. This is contrary to the previously accepted view that the follicular apparatus is the result of downgrowth of the germinal epithelium covering the ovary into the mesenchyme beneath in the form of medullary cords. In either event there is further differentiation of the cells of the sex cords into two types, one becoming the oögonia, the other the follicular epithelium, the latter grouping themselves around the egg cells to form the primordial follicles. In this process, rests of granulosa cells may be left over and from them the granulosa cell tumors arise and not from the granulosa cells of the adult follicles.

The granulosa cell is a typically feminine cell, producing the female sex hormone (folliculin or theelin); therefore, the effects produced by this type of tumor are along the lines of feminization, with overaccentuation of certain female sex characters and functions. When the tumors arise in elderly women, as they usually do, they produce a remarkable effect on the uterus, through the endocrine action of the granulosa elements. The uterus becomes characteristically increased in size and pseudomenstrual bleeding is noted, so that in some cases women far beyond the menopausal age exhibit an apparent reëstablishment of the menstrual function. This sequence must, therefore, be kept in mind as a possible explanation of postmenopausal bleeding. If diagnostic curettings in such cases show no suggestion of malignancy, but on the other hand reveal typical hyperplasia of the endometrium, the first thought should be of granulosa cell tumor of the ovary. (Curetting may also exhibit the normal cyclic changes despite the fact that the patient may have been long past the menopause.—C. C. N.) In a few cases, granulosa cell tumors have occurred in children, producing remarkable hormonal effects. The hyperfeminizing influence of these neoplasms is shown by the fact that in young children precocious puberty and menstruation are produced together with such secondary sex characters as mammary hypertrophy, the growth of genital and axillary hair, increased growth, the development of the typical feminine postpuberal contour and increased size of the uterus. Although these tumors are malignant, the degree of malignancy is in most instances very low and recurrences are exceptional, even after the removal of only the affected ovary. In a certain proportion of cases, however, the tumors have run an extremely malignant course with recurrence, metastasis and death. Such a course has been noted in between 5 and 10% of reported cases.

Schulze[5] has found 4 cases of granulosa cell tumor among 43 ovarian carcinomas occurring in 7500 gynecologic cases over a period of 19 years and has had 2 other specimens brought in from outside sources. Four of the specimens were originally diagnosed as medullary carcinoma by competent pathologists. She states that this error is not uncommon, since the microscopic illustrations of medullary carcinoma or solid carcinoma in almost any of the standard texts may be taken as fairly typical examples of the cylindroid type of the granulosa cell tumor. These tumors are usually unilateral and the majority are comparatively small in size, varying from almost microscopic ones discovered accidentally to those of the size of a man's head. They are usually well encapsulated with a thick, fibrous capsule. On cut section there appear macroscopic cysts the size of a pea, rarely up to the size of a hen's egg, containing fluid, sometimes clear, in others greenish and turbid. The greater part of the tumor is usually solid, moderately firm, sometimes friable and very vascular. Microscopically there are 3 types, the folliculoid, the cylindromatoid and the diffuse or sarcomatoid. The most easily recognizable type, and the one in which the morphologic resemblance to the normal granulosa cell is most striking, is the folliculoid and it is also the rarest. The cylindromatoid tumors are far more common but are much more difficult to recognize. They are frequently diagnosed as medullary carcinoma or solid carcinoma or even as endothelioma or sarcoma. In a few cases there may be a diffuse picture resembling a sarcoma. The epithelial cells lose their

normal characteristics and become rather hard to differentiate from the stroma cells which may show a sarcomatoid proliferation. A careful study of the patient from the endocrine standpoint will prove of aid in the pre-operative diagnosis as well as in postoperative prognosis, since these tumors elaborate follicular hormone. Schulze believes it is probable that the follicular hormone tests will become as important for these cases as is the Aschheim-Zondek test for chorionepithelioma.

An interesting case of granulosa cell tumor in a child, aged 7, who showed sexual precocity has been reported by Bland and Goldstein.[6] This child menstruated regularly, had enlarged breasts and pubic and axillary hair. She came to the hospital because of an enlargement of the abdomen and at operation a large tumor of the left ovary was removed which proved to be a granulosa cell tumor. The right ovary appeared normal and was left *in situ*. Following the operation the child did not menstruate for 18 months. The menses then returned, the abdomen again enlarged and she developed pain in the right side. At operation a tumor was removed on the right side similar to the one which had been removed on the left. She made a satisfactory recovery and on the 14th day after operation the estrin and Aschheim-Zondek tests, which had been positive before operation, became negative. Six months later, although the estrin test remained negative, there had been no regression of the mammary development and pubic and axillary hair was present in abundance.

For those especially interested in these tumors the paper of Brewer and Jones[7] reporting 3 cases and that of Daily[8] presenting 2 cases may be consulted for further case details.

In considering the treatment of these tumors, Novak and Brawner[9] state that it is essentially surgical. The extent of the operation must be based upon our concept of the degree of malignancy which is concededly less than that of other ovarian neoplasms. Many patients have remained well after simple unilateral salpingoöphorectomy, but they believe that such a conservative plan should be followed in only a limited group in view of the fact that recent reports indicate a greater degree of malignancy than had been previously assumed. In young patients the removal of the adnexa on the affected side alone would seem permissible, but such patients should be carefully followed for evidence of recurrence. In the more common case, in which the patient has already lived all or most of her reproductive life, the definite menace presented by these tumors would seem to justify a more radical procedure, namely, hysterectomy with bilateral removal of the adnexa. This would certainly apply to the frequent cases seen in women beyond the menopause. In view of the sensitivity of granulosal tissue to radiotherapy, it would be expected that these tumors should likewise be very responsive to this form of treatment, although only a few reports have been made on this point. They believe, however, that for the present it should seem wiser to restrict radiotherapy to the treatment of inoperable or recurrent tumors, or to combine it preoperatively of postoperatively with surgery in the treatment of removable tumors.

Krukenberg Tumor. This neoplasm to which the unwieldy name, "fibrosarcoma ovarii mucocellulare (carcinomatodes)," is applied should be of passing interest to every practitioner if for no other reason than its name. Krukenberg described it as a fibrosarcoma and believed

that it was primary in the ovary, although there has been considerable discussion about this. In presenting 3 cases of this type Andrews[10] states that it is a solid ovarian tumor, usually bilateral, maintaining the contour of the ovary. It is pale gray and heavy, usually associated with ascites. The microscopic picture is that of a dense fibrous tissue in the meshes of which are the characteristic cells with nuclei displaced eccentrically, giving a signet-ring appearance. The tumor is generally regarded as a carcinoma. At present most authorities concede that these tumors are always secondary to carcinoma in the upper abdomen but the mode of transmission is not definitely settled, since some believe it arises from direct implantation on the ovary while others believe it is transmitted by lymphatic channels.

Based upon 5 certain and 7 additional probable cases of Krukenberg tumor which have been seen at the Mayo Clinic, Masson[11] is also of the opinion that these tumors are usually bilateral and retain the form of the ovary. They are probably always secondary. Of the patients in this series whose subsequent history is known, all have died of the disease. He feels sure that in many cases of general abdominal carcinomatosis in which exploration is made late in the disease, the typical pathologic change in the ovarian tissue is not evident. The picture is obscured by necrosis and cystlike formations, which develop because circulation for the rapidly growing tumor is inadequate. Furthermore, ovarian tumors are often removed as solid carcinomas or sarcomas, and when death ultimately occurs, as it invariably does in this condition, necropsy is not performed, and death is credited to recurrence of the ovarian tumor, or to metastasis from it. If necropsy had been performed, in many of these cases a malignant growth in the gastrointestinal tract probably would have been found. He believes that these tumors are of more frequent occurrence than the literature would indicate, for they are seldom diagnosed before operation or necropsy and often not even then. (When operating upon patients for ovarian neoplasm, especially if the tumor is thought to be malignant, the entire peritoneal cavity should be explored.—C. C. N.)

Presenting a Krukenberg tumor with rectal involvement, Runyeon[12] states that such a complication is very rare, only a few having been reported in the literature. In reviewing Krukenberg tumors in general, he has collected 91 cases in 23 of which only the ovary was involved. He asks, therefore, why it is necessary that the ovarian picture must always be a secondary one. He believes that a carcinoma of this type may originate in the ovary primarily in certain cases, and by its presence stimulate the connective tissue cells of the ovary to the same growth that is produced by a carcinoma originating in the stomach and secondarily involving the ovary. This is, of course, contrary to most opinions.

Arrhenoblastoma. A rare but exceedingly interesting tumor, which at times produces effects on sex characters almost diametrically the opposite of those resulting from granulosa cell tumors, is the arrhenoblastoma, which has a masculinizing effect on the patient. Novak and Long[4] state that the histogenesis of these tumors is to be sought in certain undifferentiated cells persisting in the rete and capable of later function along either male or female lines. To put it another way, every woman shelters within the medulla of the ovary a potential testis. Under certain conditions this undifferentiated male tissue may become active, and its male endocrine influence may override the primary

female tendency. The clinical manifestations of these tumors vary according to the degree of their masculinizing hormonal influence, and this in turn appears to be a reflection of the degree of undifferentiation of the tumor cells. In the most extreme cases the woman who has previously been of normal feminine type becomes amenorrheic, the breasts flatten and atrophy, a heavy growth of hair appears over the face, chest, abdomen and lower extremities, the figure loses its normal feminine curves and assumes the typically more angular contour of the male and the voice becomes much deeper, owing to laryngeal hypertrophy. The clitoris may show such hypertrophy as to be almost penis-like in its proportions. Such symptoms occurring in a patient who has developed an ovarian tumor should lead to the suspicion that one is dealing with an arrhenoblastoma. Removal of the tumor leads to a regression of the symptoms, thus establishing its causative rôle. Tumors of this general group are usually unilateral and, like most tumors of this embryonic group, are of a relatively low degree of malignancy. Only a small group of these tumors has been reported, but with new interest in the syndrome there is little doubt that the number will be rather rapidly augmented. The case reported by Mathias[13] is of especial interest in that after removal of the tumor there was a subsequent pregnancy, there being only 4 similar cases in the literature. In this case a girl, aged 17, had an amenorrhea of 2 years' duration, during which time masculine characteristics developed, including a growth of beard, male type of pubic hair, loss of feminine contour, alteration in voice and enlargement of the clitoris. After the removal of an arrhenoblastoma, most of the secondary male characteristics disappeared. The patient subsequently conceived and was delivered by section because of the male type of pelvis.

Other Rare Tumors. A third type of tumor which alters the sexual characteristics of the afflicted person, differing from both the granulosa cell tumor and the arrhenoblastoma is the theca cell tumor or "fibroma thecocellulare xanthomatodes ovarii." Two cases of this type have been reported by Melnick and Kanter,[14] who state that there have previously been reported only 6 similar cases. These tumors are of the feminizing type and, like the granulosa cell tumors, produce glandular hyperplasia of the endometrium, together with more or less periodic bleeding in postmenopausal women and amenorrhea in younger women. Such effects are undoubtedly due to the secretion of estrogenic hormone by the tumor. The site of origin of this hormone (theelin) is still a point of discussion. The Graafian follicle, particularly the granulosa cells, has been considered to produce the hormone, but these authors believe that there is much evidence that the cells of the theca interna play a rôle in its production. While the function of the theca interna has been much of a mystery, its activity in the ripening follicle, in the young and degenerating corpus luteum and in the atretic follicle indicates that it has a possible function. In the cases described, the tumors arose from the cells of the theca interna and since they exerted a distinct hormonal effect, they believe that the theca cells take part in the production of theelin.

The occurrence of a *squamous-cell epithelioma* in a *dermoid cyst* of the ovary is unusual. Counseller and Wellbrock[15] found 7 (1.7%) in a series of 408 dermoid cysts which proved grossly and microscopically to be associated with primary epithelioma of the epithelial elements

of the cyst. Of passing interest it may be noted that 88 of the other cysts contained only sebaceous material; 192, sebaceous material and hair; 76, teeth in addition; while 45 contained hair, cartilage, bone and calcareous material. Discoursing upon the confusion that exists as to the proper classification of dermoid cysts, they believe that they are properly classed as cystic teratomas. A true dermoid cyst is a distinctly inclusion cyst, such as those seen in the coccygeal, perineal and branchial regions and contains products from the ectoderm only, whereas the cystic teratoma contains tissues derived from one or all three germinal layers. Solid teratomas resemble the cystic teratomas in that they are usually composed of all three germinal layers. The true point of distinction is that the tissues composing the solid teratomas are of the early embryonal stage and do not reproduce the highly developed and differentiated bodily structures which may be seen in the cystic tumors. The solid teratomas are much rarer than the cystic and are extremely malignant. The Reviewer recalls the only case of solid teratoma which he has seen and which recurred as an extensive growth within a month after removal of the primary tumor.

In reporting an *ovarian tumor which contained thyroid tissue* Lyday[16] states that, although the incidence of this type is supposed to be about 2% of all ovarian tumors removed, a relatively small number have been recorded in the literature. The case he reports is that of a girl, aged 19, in whom an ovarian tumor was discovered by routine examination. At operation a large multilocular cyst of the left ovary, weighing $8\frac{1}{2}$ pounds, was found. At the base of the tumor near the pedicle was a solid portion, about 2 inches in diameter, which upon microscopic examination showed typical thyroid tissue. There were no symptoms in this case referable to hyperfunction of thyroid tissue.

Fibroma of the ovary, while a benign tumor, is often confused with a malignant condition because it is frequently accompanied by an ascites. An interesting case has been reported by Marshall and Swanton.[17]

Prognosis of Ovarian Cancer. According to Judd and Phillips,[18] on opening the abdomen in a case of carcinoma of the ovary, a surgeon's first impression may be that the malignant process is too extensive for the condition to be remedied. However, in many instances careful dissection will afford a chance for palliative relief and in such cases the patients have lived over 5 years. Even in the most hopeful cases, adequate treatment will include removal of the uterus, tubes and ovaries. Metastasis is usually by direct extension or by implantation. Papillary cystadenomas, in particular, have a tendency to rupture early in their course, and numerous nodular growths may develop. If secondary growths are present, as many as possible should be removed. In some cases the body of the uterus will be involved; therefore, hysterectomy should be included in any operation. If there should be a recurrence of the pelvic tumor at some later date, a second operation may be justified. Often removal of such a lesion will so completely control the disease that the patient is able to live for the normal span of life. They believe that the prognosis depends on many factors. The grade of the ovarian malignancy is one of the important determinants, since each of 2 patients who had adenocarcinoma of the ovary, graded 1, has lived more than 16 years since operation. An intracystic process is more likely to be controlled than one that is extracystic. In both cases in which the tumor was graded 1, the condition was bilateral,

and in one of these the growth was not only extracystic but had ruptured and produced multiple implants. It has been shown that in about 25% of the cases the disease will be bilateral. Because of the lapse of this length of time, and because both of these patients are entirely well at present, they believe that they will continue to be free from the disease and will have many additional years to live, as they are now aged only 51 and 52 years.

Irradiation Therapy of Ovarian Cancer. Backed by a most extensive clinical experience, Healy[19] is of the opinion that ovarian tumors should be treated surgically unless there is some contraindication to operation, since it is often difficult to differentiate clinically between a benign and a malignant ovarian tumor and surgical removal of the former should always result in cure. If at operation the tumor is found to be malignant but is apparently completely removed, postoperative irradiation of the entire pelvic and tumor field with high-voltage Roentgen ray should, nevertheless, be done within from 4 to 8 weeks. Such treatment should always include the line of incision, because of the frequency of incisional recurrences from implantation metastases. This series of Roentgen ray treatments should be repeated 2 or 3 months later. If the tumor is malignant, and at operation is only partially removed or not removed at all, intensive postoperative irradiation of the entire tumor field with high-voltage Roentgen ray should be established as soon as the condition of the patient will permit. If the tumor masses respond to radiation but do not disappear, the series of treatments should be repeated as soon as the condition of the patient's skin in the irradiated fields will permit and as often thereafter as may seem to be necessary. If the clinical findings indicate that the tumor is probably malignant but is too extensive for operation, radiation therapy with high-voltage Roentgen ray or the radium pack should be intensively carried out. If thereafter sufficient improvement is obtained, surgical interference may be then instituted. Tumors complicated by large quantities of free fluid or metastases should be intensively irradiated and observed for a time before resorting to exploratory operation, as the tumor masses will, in many instances, diminish markedly in size and occasionally may disappear entirely. Free abdominal fluid, if present in sufficient quantity, should always be removed by paracentesis before radiation treatment is given and as often as may be necessary during the course of treatment.

Montgomery and Farrell[20] have analyzed 22 cases of ovarian carcinoma according to type, grade of malignancy, operability and response to postoperative Roentgen ray treatment. Of 11 patients observed more than 5 years, 5 (45.4%) are alive. Of 14 patients with papillary cystadenocarcinoma, 7 are living and 7 are dead; 3 patients had papillary adenocarcinoma, 1 is living and 2 are dead; 4 patients with adenocarcinoma are dead; 1 patient with granulosa cell carcinoma is living. In order of malignancy, the granulosa cell is the least malignant, the papillary cystadenocarcinoma the next, the papillary adenocarcinoma is more malignant than the preceding and the adenocarcinoma is the most malignant. They also believe that the histologic grading of malignancy is important in the prognosis of ovarian cancer. Only 1 patient in their series whose tumor was of high-grade malignancy has survived for more than 5 years; all others with tumors of intermediate or high-grade malignancy are dead. They state the obvious fact that the more

completely operable the tumor, the greater the life expectancy, and they have also found that postoperative Roentgen ray irradiation is often of value in relieving pain and ascites and in reducing the size of the tumor. A comparison of this series of patients treated with postoperative irradiation and a group treated by operation alone indicates that the duration of life is longer in the irradiated patients, so that they urge postoperative irradiation in every case, no matter how hopeless the prognosis, if the general condition of the patient will permit. In the discussion of this paper Keene presented his observations on 38 cases which he divides into 3 groups: (1) Advanced lesions with advanced peritoneal carcinomatosis, in which the primary growth could not be removed; (2) removable growths, but peritoneal metastases present; and (3) the early cases where the growth could be completely excised and there was no visible evidence of extension. Twenty-one patients are dead and all belonged to Groups 1 and 2. In 90% of these, death occurred in 2 years or less after the beginning of their treatment. In his experience the histologic grading has been of little or no value in prognosis. He found that postoperative irradiation diminished or relieved pain in 60% of the cases. Ascites was present in 22 cases, and in one-third of these accumulation was retarded, thus lengthening the interval between tappings and, in a few, it was entirely checked. Abdominal masses were reduced in 30% and in some they completely disappeared for a time. These results seem to justify the conclusion that Roentgen ray irradiation is of value as a palliative measure. His experience has also shown that even in the presence of peritoneal metastases, the primary growth should be removed whenever possible. The advisability of combining deep Roentgen ray therapy with operation in the early cases is still controversial, but the evidence at hand strongly indicates that by combining the two, the total 5-year salvage will be increased.

In this same discussion Widmann stated that at the Philadelphia General Hospital they have not discovered anything that will control the untoward symptoms which accompany intensive irradiation. Intravenous glucose and sometimes normal saline seem to have been beneficial. He does not believe that anemia is a contraindication to irradiation, since patients with red blood cell counts as low as 2,000,000 and a hemoglobin as low as 25% will tolerate radiation given cautiously. On the other hand, a white blood cell count less than 3000 seems to be the most decided contraindication. In the very profound anemias he believes it worth while to consider transfusion for transient benefit.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF
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TUBERCULOSIS OF THE SKIN.

RECENT PROGRESS IN THEORY AND PRACTICE.

Pathology and Immunology. The principal contributions of the past 2 years in this field have included a further report by Kren and Lowenstein[1] on the cultivation of tubercle bacilli in the blood of patients with various forms of clinical tuberculosis and tuberculid; the discussion of the significance of anergy in relating such conditions as sarcoid of Boeck to cutaneous tuberculosis (Jadassohn[2]); the observations of Kallos and Nathan[3] on some cultural peculiarities of the tubercle bacillus from human cutaneous tuberculosis; the significance of the epicutaneous or tuberculin patch tests in diagnosis and as a measure of tuberculin allergy by Hruszek[4] and Sipos;[5] and finally the discussion conducted at the reunion in Strasbourg by a large group of French-speaking dermatologists on the etiology of sarcoid and its possible relations to tuberculosis and other conditions.

Summarizing this work, it appears that Kren and Lowenstein, who originally announced 75% positive cultures of tubercle bacilli from the blood by a special method in cutaneous tuberculosis of various types, have conducted 377 further examinations of 101 cases of cutaneous tuberculosis and 32 cases of lupus erythematosus. These authors contend that the usefulness and applicability of their method has been supported by other reports in the literature, including 18 positive cultures in cadaver blood and 12 from the blood of living patients with cutaneous tuberculosis. They obtained in their second series 51.8 positive cultures; 20% positive on a single trial and 100% positive on cases subjected to 4 cultural attempts. This work must be rated as still unconfirmed. Jadassohn,[6] both in independent publication and before the Strasbourg reunion, pointed out the striking resemblances between the characteristic anergic cutaneous reactions to tuberculous

inoculation in rats and human sarcoid. He pointed out that not only did tubercle bacilli rapidly disappear from the site of inoculation in an anergic animal or individual, but that the organisms which remained were rapidly changed in morphologic characteristics. The histologic reactions were very suggestive of sarcoid. He, therefore, considers that it is justifiable to interpret human Boeck's sarcoid as a form of anergic tuberculosis in man. Kallos and Nathan showed that only the serum of patients with cutaneous tuberculosis can inhibit growth and change the morphology of tubercle bacilli cultivated in cutaneous lesions. Serum from patients with pulmonary tuberculosis has no effect. The serum from patients with lupus erythematoides and Boeck's lupoid had no effect on cutaneous strains of tubercle bacilli. The work was performed on laboratory strains and could not be confirmed on tubercle bacilli cultivated directly from the human cutaneous lesions.

The observations of Kallos and Nathan on the specificity of patch test performed with 10% old tuberculin on patients with cutaneous tuberculosis as a means of diagnosing tuberculous lesions, have been subjected to further study, and the prevailing opinion is that the tuberculin patch test, when positive, is a measure of the grade of allergic susceptibility to tuberculin in the individual but does not require the presence of a cutaneous tuberculous lesion for a positive reaction.

Epidemiology. Ledermann,[7] in studying the incidence and proportion of tuberculosis of the skin in the clinics of Breslau, made the observation that there was a marked decrease in fatality of tuberculosis in Prussia up to the time of the World War (31 per 10,000 to 14.5 per 10,000) with a reversal of the trend or increase of frequency following the war. In Breslau there was a marked increase of both cutaneous and glandular tuberculosis from 1913 to 1919, with a recession following the siege of 1918–1920. Tuberculosis verrucosa cutis, however, was an exception and did not increase in frequency because of the war. The author pointedly remarks on the unreliability of epidemiologic figures based on clinic attendance, for it was distinctly observed that the picture of tuberculosis as seen in the clinics was influenced by the movement of physicians back to the country after the war, with corresponding changes in clinic attendance.

Various Clinical Types of Cutaneous Tuberculosis. *Erythema Nodosum.* The relation of the more or less non-specific clinical picture of erythema nodosum to tuberculosis is arousing widespread interest. For a number of years the closeness of this relationship in infants and young adults exposed to tuberculosis has been more or less recognized, but lacked precise definition. In an editorial in the *Lancet* (**2**, 660, 1934), the entire problem is reviewed. Four types of the condition are recognized: (1) A form which may be regarded as an infectious disease *sui generis* and more properly called nodal fever; (2) a type associated with acute or subacute rheumatism; (3) the tuberculous type; (4) a type due to various toxins, especially from streptococci. Slot[8] believes that in London at least the majority of cases are due to streptococcal and not to tuberculous infection. This view is vigorously opposed by Forman and Whitwell,[9] of Guy's Hospital, who quote Symes as finding that 10% to 20% of erythema nodosum patients subsequently developed tuberculosis, the period of greatest danger being 6 months after the appearance of the nodes. Symes quotes the Scandinavian incidence as being in some cases as high as 50%, but most frequently 10% to

30%. He cites Wallgren,[10] who obtained tuberculous infections in guinea pigs by inoculating them with the washings of the stomachs of children with erythema nodosum. The fact that the erythema nodosum precedes the appearance of frank tuberculosis explains the relative rarity of the condition in the frankly tuberculous individual. Lendon observed 40% phlyctenular conjunctivitis in his cases and Symes, 10%. Forman and Whitwell conclude that erythema nodosum is a reaction to bacterial allergy and do not subscribe to the rheumatic or streptococcal etiology so far as England is concerned. They point out the futility of pathologic and bacteriologic studies of the nodes because of the presumed small number of the bacilli and the rapid bacteriolysis which occurs in the inflammatory allergic reaction. The frequent initial severe sore throat these authors believe activates the tuberculous focus. They subscribe to Ranke's view that erythema nodosum is a secondary tuberculous manifestation with the probable course of events including a primary inoculation with tubercle bacilli usually *via* the respiratory tract, but occasionally through the skin or other structures. The patient becomes acutely allergic as a result of this inoculation, where erythema nodosum ensues, but in the case of miliary tuberculosis a depressed sensitivity to tuberculin develops. Comparing the child with erythema nodosum with the adult with erythema induratum, the authors believe that erythema nodosum is a manifestation of a high degree of allergic susceptibility, while the chronic erythema induratum, in which tubercle bacilli have been found, is an expression of late slight allergic reaction in a patient primarily infected years before.

In the Scandinavian countries the acceptance of erythema nodosum as tuberculous is apparently quite general, whereas the German school is inclined to oppose the conception. Giertsen[11] studied 93 cases in Bergen, from 1924 to 1931, of which 87% were between the ages of 15 and 30; and a marked adenitis at the hilus of the lung was found in 80% of 89 patients. In 48 of these cases pulmonary infiltration or pleurisy was found within the first month after the appearance of the erythema nodosum. Pathologic changes at the apices were rare. The Pirquet test was positive in 46 of 47 cases. The sedimentation test was very valuable, an increased rate of sedimentation more than a month after the nodes had appeared being interpreted as evidence of active disease of the lungs or pleuræ.

Ernberg[12] has studied 200 cases of erythema nodosum at the Sachs Children's Hospital in Stockholm, and concludes that erythema nodosum is to be regarded in general as a symptom complex of tuberculous nature. The focus is usually in the region of the pulmonary lymph nodes. It is essentially an autogenous tuberculin reaction, characterized by a general, local and focal phase, including fever, the characteristic eruption, and a focal reaction in the hilar region. It appears most often as a very early stage of tuberculosis in the transition from the preallergic to the allergic state. In some cases an infectious disease may precipitate the allergic condition. In treatment it is important to estimate the condition of the pulmonary lymph nodes. The prognosis is usually favorable, and it is frequently possible to trace the source of infection to a formerly unknown carrier, namely, a person with open tuberculosis. Rotnes[13] publishes independently confirmatory evidence of the open tuberculous source of infection in erythema nodosum in his description of a "family epidemic," in which 4 sisters living together,

2 children and 2 adults suffered within 5 weeks from acute and typical erythema nodosum. In both children a probable fresh lung infection was detected radiologically. Both adults were free radiologically. All 4 gave strong cutaneous tuberculin reactions. Shortly before the attack, 1 child and 1 adult had been found Pirquet-negative and also with lungs free radiologically. No throat or rheumatic symptoms were found in any case. The tuberculous husband of 1 of the grown-up sisters had recently come to live in the house, and before his death, a few months later, he infected 3 children additional to the above. The author concludes that the erythema nodosum was of the same nature in all 4 cases; that tuberculous infection was an essential condition for its development and that in no particulars did it differ from classical "idiopathic" erythema nodosum. In Cruise's[14] careful study of 33 cases of erythema nodosum in pupil nurses, ⅓ either developed definite tuberculosis or were suspicious of tuberculosis either at the time of the eruption or within 6 months; and over ½ had erythema nodosum during or after their affiliation with an institution for the treatment of tuberculosis. Cruise, as a result of this investigation, rates erythema nodosum as fully as much a manifestation of tuberculosis as pleurisy with effusion. One nurse developed active tuberculosis of the lungs within 6 months after having acute erythema nodosum and succumbed within another year. Similar cases have been mentioned in the American literature during the past decade, and Holmes[15] states that in the Frederiksburg Hospital, Copenhagen, in Pirquet-negative nurses exposed to tuberculous infection, 22.1% developed erythema nodosum within 7 months from the first date of exposure. This résumé does not by any means include the full roster of publication during the past several years on this topic, so that the volume of evidence for a tuberculous factor is larger even than here presented.

Primary Inoculation Tuberculosis. The rather scanty literature on this subject is reinforced by a careful report from Siegl.[16] The 5 children all presented negative pulmonary examinations, both clinical and radiologic, blood stream infection was excluded and the conspicuous and sharply reactive lymphatic metastasis was easily identified. Siegl believes that a negative tuberculin test does not exclude systemic tuberculosis in these cases, but points out that the clinical picture of primary inoculation tuberculosis is easily recognized by the very marked lymphadenitis, which does not occur in local inoculation of the exogenously infected tuberculous child (as in the case of tuberculosis verrucosa from thumb sucking which he cites). In tuberculosis verrucosa cutis, no regional lymphadenopathy is observed. The article is accompanied by a number of excellent illustrations. Ledermann[17] disagrees on the matter of local lymphadenopathy which he says is marked in tuberculosis verrucosa cutis. This form of inoculation tuberculosis was found to occur chiefly in farmers and laborers, usually on the hands, and to be, in 60% of cases, of the bovine type.

Lupus Erythematosus. The relationship of this condition to tuberculosis was studied by Keil[18] on the basis of the recorded 125 postmortem examinations of patients with lupus erythematosus, plus 20 in the author's own series. From the literature only 20% of autopsies show active or possibly active stigmata of tuberculosis. From the necropsies personally studied as well as those afforded in the literature, Keil comes to the conclusion that the occurrence of tuberculosis in cases

of lupus erythematosus is only coincidental, and that there is no justification for the assumption that active tuberculosis is present merely because the patient has lupus erythematosus. No account is apparently taken in this study of the significance of allergic states.

Sarcoid of Boeck. This disease, the clinical manifestations of which range from papular eruptions to bluish tumors and infiltrations of the skin with a tuberculoid architecture, has long been the battle ground in the discussion of tuberculous etiology. The 1934 Strasbourg reunion[19] devoted practically its entire session to the consideration of this question. At the close, Pautrier surveyed the confused terminology, eliminating miliary lupoid from the conception of sarcoid, and likewise the deep subcutaneous sarcoid of Darier-Roussy. He pointed out that the sarcoid originally described by Boeck was a generalized disease affecting the skin, bones, glands and lungs and that in this conception, Schaumann's benign lymphogranulomatosis and the Besnier-Tenneson *lupus pernio* could be regarded as varieties of the same disease. Even Pautrier's attempt at terminologic reconciliation provoked disagreement, in which Darier considered that sarcoids presented a multiple etiology and Nicolas and Gaté did not believe that the deep sarcoid of Darier-Roussy could be decisively separated from the sarcoid of Boeck. Kissmeyer insisted on the resemblance of the condition to leprosy rather than tuberculosis; Schaumann supported the tuberculous etiology; and Ramel and W. Jadassohn spoke in favor of the tuberculous etiology. Hollander and Schlesinger[20] summarize the blood picture in 4 patients from the standpoint of a possible tuberculous etiology, with an inclination to classify the disease as tuberculous.

Granuloma Annulare. This condition has been one of the long-standing puzzles of dermatologic etiology. Michael[21] has produced a massive review of the literature of the etiology of *granuloma annulare*, from which he concludes (including the evidence from 8 cases of his own) that in some cases its tuberculous origin seems well supported, but that in a larger proportion it is not. In other words, it is still an infectious granuloma of unknown origin. Bertin,[22] at the Strasbourg reunion, draws essentially the same conclusions from his observations.

Michelson and Winer[23] pass some interesting comments on tuberculosis of the skin as it appears on the face. They emphasize the need for examining at least 25 sections from any biopsy for an adequate histologic appraisal, and frankly state that the histology of the various types of tuberculous lesions of the face is entirely inadequate for the drawing of sharp lines of differentiation. During the lymphocytic and exudative phase of the involution of individual lesions bacilli can frequently be found, but in the tuberculoid period they have been destroyed. Early lupus vulgaris is sometimes difficult to diagnose, for it looks more like a chronic diffuse inflammation. Central necrosis and caseation is not a necessity for the diagnosis and remnants of bloodvessels will usually be found at or near the center of the lesion. Most cutaneous tuberculosis may be looked on as arising from a hematogenously borne infection.

Treatment of Cutaneous Tuberculosis. From the very large literature on this topic, the account given by Funk[24] gives a particularly clear résumé of current conceptions. He estimates that there are 50,000 cases of cutaneous tuberculosis in Germany. Emphasis must be on the use in each individual case of every available constitutional measure in

addition to the complete destruction of the individual lesion. His estimate of the Sauerbruch-Hermannsdorfer-Gerson salt-poor diet is particularly interesting. He states that in from 6 to 24 months complete healing of lupus vulgaris can be secured by this dietary procedure, which he says surpasses even the Copenhagen light therapy in effectiveness. There are, however, diet refractory cases, and the necessity for following the prescribed dietary régime *exactly*, in amount, quality and character of food, makes it essentially an institutional procedure. The calorific requirements range from 2800 to 3000, with a protein-fat-carbohydrate ratio of 90 to 160 to 240. Its cost and the difficulties of preparation make it available to relatively few. In discussing light therapy, Funk emphasizes the caution necessary in cases of visceral involvement and stresses Rollier's plan of exposing the skin to air for some time before beginning the sun cure. The gradual exposure of increasing areas of the skin, the necessity for urinalyses, protection of head and eyes, and introduction of periodic rest periods for depigmentation are less familiar points. He speaks highly of tuberculin, emphasizing the necessity for watching possible visceral foci and commenting on the occasional extensive necroses with the sloughing out of an entire lesion, which occur under tuberculin therapy. He rates the bacillary preparations as worthless, including Friedman's vaccine. The technique which he employs is essentially that of Doutrelepont and Zieler, with a test dose of 0.01 to 0.1 mg. O T intradermally, increased to 0.25, 0.5 and 0.75 mg. intramuscularly. Hoffman begins with 0.002 to 0.5 mg., increasing very slowly. In discussing surgical excision, which he recommends as in the main the most satisfactory method for completely removing the cutaneous tuberculous focus, he recommends irradiation of the scar with ultraviolet light, under pressure, and the necessity for absolute and deep obliteration of the affected tissue, on account of the presence of small deep vascular foci. High frequency current is very satisfactory for excision purposes. Plastic restorations following surgical removals must be avoided except after years of satisfactory healing. The excision of a tuberculous area in the skin should not be attempted under local anesthesia, on account of the frequent unexpected necessity for deep excision. Pyrogallol and ointments are rated as suitable only to small lesions on the face and should always be combined with light therapy and the SHG diet. Funk commends the Pfannenstiel method of treating mucosal tuberculosis by the internal administration of sodium iodid with a gargle of hydrogen peroxid. Certain proprietary lipoiodin preparations can also be used in conjunction with the hydrogen peroxid, their effect presumably being to liberate nascent iodin in the tissues.

An equally valuable review of the treatment of lupus vulgaris from the Scandinavian standpoint is that of Lomholt.[25] The incidence of lupus vulgaris is rated by him as approximately 1 to 1000 in Denmark, and approximately the same in Germany. Direct inoculation is rare and produces only small and benign lesions. The extension may be from a suppurative lymphadenitis, a colliquative tuberculosis of the skin, especially in children, and from the region of tuberculous fistulæ. Hematogenous and lymphogenous transplants from tuberculous foci in the lungs, lymph nodes and mucosa of the nose are rated as the most important. Patients with pulmonary tuberculosis seem fairly immune.

Lupus vulgaris is bovine in origin in 40% of cases, but there is no clinical difference in the course of the bovine and human type.

Eighty per cent of cures are obtained with Finsen light treatment with the concentrated carbon arc supplemented by carbon arc light baths. In early cases, with small lesions, the recovery is rated at 100%. The experience of the Finsen Institute with the Gerson diet in 40 patients, on whom it was used, was unsatisfactory, but a high vitamin diet was recommended. Like Funk, Lomholt recommends surgical excision as the most certain and successful method; with electrocoagulation, the risk of recurrence is less, but the scar more conspicuous. Scarification is rated as relatively ineffective; chemical corrosives including pyrogallic acid remove most of the diseased tissue but rarely result in complete recoveries. The scar, moreover, is apt to undergo disfiguring hypertrophy, which also makes subsequent light treatment much more difficult. Treatment with the Kromayer water-cooled mercury vapor lamp is rated as less expensive but inferior to the Finsen light. The details of the Finsen method are fully given. Roentgen ray and radium are rated as giving a good transitory symptomatic effect, but definite cure is rare and Roentgen ray sequelæ common. In this connection, Hesse[26] attacks Roentgen ray as the most dangerous and unsatisfactory of all methods by arguments which are seemingly incontestable.

An interesting theoretical discussion of the mechanism of the SHG diet is that of Bommer.[27] He remarks that the disappearance of inflammation is characteristic of the SHG diet—the precise opposite of the tuberculin method of treatment and that the degree of healing under the diet depends on the degree of disappearance of the inflammation. He has observed benefit to skin injuries from Roentgen ray by placing patients on the SHG diet, the involution and paling of hypertrophic scars and recovery from an extensive vasomotor lividity in an individual case. From these observations he concludes that the effect of the SHG diet is on the vascular system and perhaps on the water balance of the body, and that the diet is, therefore, essentially a method of treating the vascular abnormality which underlies the tuberculous manifestations.

Tuberculin treatment of lupus vulgaris received strong support from the observations and experience of Aitken.[28] He cites particularly the work of the Edinburgh group, headed by Norman Walker, as a fairly conclusive demonstration of the great value of tuberculin therapy in treating lupus vulgaris. Spiethoff[29] briefly summarizes his technique of the treatment of lupus vulgaris with the Bucky Grenz irradiation, though he gives no precise statement of results. Large doses are necessary, the average being 4600 R with 9 kv., 2.5 cm. skin-window distance, and in some cases a dosage ranging as high as 6200 and 9200.

Areas larger than 3 cm. are not satisfactorily treated at a single exposure. In hypertrophic cases, a field of 2.5 cm. with 1 cm. skin-window distance and 28,750 R has been employed. The cost is less than Roentgen ray, the chief source of expense being damage to the windows of the apparatus. The method must be regarded as still unevaluated.

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(Titles have been omitted for sake of brevity.)

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Observations on Adrenalectomized-depancreatized and Hypophysectomized-depancreatized Cats. C. N. H. Long and F. D. W. Lukens (George S. Cox Medical Research Institute, University of Pennsylvania). Adrenalectomized-depancreatized or hypophysectomized-depancreatized cats in the fasting state excrete less glucose and nitrogen than totally depancreatized animals. Furthermore, the intense ketonuria which is such a characteristic feature of depancreatized cats does not appear in the doubly operated animals and, in fact, is absent throughout the remainder of life unless measures are instituted that cause its appearance.

The survival of 15 adrenalectomized-depancreatized cats has been from 5 to 28 days while 8 hypophysectiomized-depancreatized animals have survived from 18 to 85 days. The average survival of 16 depancreatized cats was around 4 days.

Removal of one adrenal and denervation of the other does not alter the diabetic condition in the cat. This suggests that the adrenal cortex rather than the medulla is responsible for the changes observed following total adrenalectomy. In addition the fact that hypophysectomy causes regressive changes in the adrenal cortex but not in the medulla is also evidence for this point of view.

The injection of anterior pituitary extract (Squibb) into hypophysectomized-depancreatized cats is followed by heavy ketonuria and if sufficient extract is given death in coma occurs in about 48 hours. The same extract when injected into a number of adrenalectomized-depancreatized cats does not produce ketonuria or coma even though amounts are administered in excess of those sufficient to kill the former group of animals.

The injection of large doses of epinephrin into animals of either type has been followed by ketonuria only once in each group. It was later found that the supposedly adrenalectomized cat had an accessory cortical nodule.

Experimental Studies in Gastric Physiology in Man. III. A Study of Pyloric Control—The Rôle of Milk and Cream in Normal Subjects and in Those with Quiescent Duodenal Ulcer. G. GERSHN-COHEN and HARRY SHAY (Laboratories of Drs. Gershn-Cohen and Shay, Philadelphia). Roentgenologic studies were made in a group of 7 normal subjects and in another group of 4 with quiescent duodenal ulcer. The effects on gastric motility with meals of water, milk and cream were studied in both groups and attempts made to analyze and compare our results with the findings of others using different materials and methods. The effects of these substances on the various intrinsic factors in the mechanism controlling gastric evacuation were studied and compared with the effects of acids and alkalis on the control of the pylorus previously reported. Our findings reaffirm the known marked delay of gastric motility caused by the ingestion of milk and cream. The direct application of milk and cream to the duodenal mucosa through a duodenal tube produced a more pronounced delay in gastric evacuation than when taken by mouth. The most marked effects of these ingested materials were noted at the beginning of digestion and were characterized chiefly by spastic contraction of the pylorus with cessation of gastric peristalsis. When this effect was intensified by direct application of milk and cream through the duodenum, spasm of the duodenal cap and antrum occurred simultaneously, all three anatomic units acting as one. As digestion proceeded, spasm of the pylorus changed from a tonic to a clonic type, opening and closing of the pylorus becoming intermittent. Gastric peristalsis gradually returned to normal and intermittent filling and contraction of the duodenal cap followed. When both the duodenal cap and pylorus were opened simultaneously, gastric evacuation ensued so that motility from the stomach was intermittent. The subjects with quiescent duodenal ulcer differ from the normal only in that after disappearance of the initial pyloric and antral spasm, gastric peristalsis was intermittently markedly intensified rather than evenly vigorous. Emptying of water was quickest in the achlorhydric and hyperchlorhydric stomachs of the quiescent duodenal ulcer group, but emptying of milk and cream was lowest in the achlorhydrics and quickest in the hyperchlorhydrics.

An analysis of the elements of gastric evacuation would lead us to believe that the pylorus can and does function as a true sphincter; that an intestinal reflex, probably through the action of a humoral agent or chalone, is one of the principal controls in this action of the pylorus during digestion; that the intensity of reflex control of pyloric action is proportionate to the fat contents of milk and cream and the iodin number of the fats; and that the sphincteric action of the pylorus is the principal element governing gastric evacuation.

It appears that the tested substances act in controlling gastric motility principally through the reflex control of the action of the pylorus very much like strong acids and alkalis, the action being more intense and longer sustained.

Duodenal and gastric peristalsis are controlled by the same reflex mechanism as the pylorus, but are not so potent a motor element in gastric motility. They are, however, definite modifying factors. Whereas gastric tone, habitus of the patient, and posture during digestion might, under special conditions, have a bearing on gastric motility, gastric acid secretory response is a more constant modifying factor.

Changes in Bloodvessel Endothelium. E. R. and E. L. CLARK (Laboratory of Anatomy, University of Pennsylvania. Illustrated by motion pictures with the assistance of E. A. SWENSON). The present studies on blood vascular endothelium were based upon microscopic observation of living bloodvessels and of the cells circulating through them, in the transparent tails of amphibian larvæ and in transparent chambers permanently installed in the ears of rabbits. In addition to prolonged observations in undisturbed vessels, the changes in blood vascular endothelium following mechanical injury and extravascular injections of minute quantities of various foreign substances (paraffin oil, carmine granules, lipoid substances, protein, starch, and dilute croton oil) were studied in the amphibian larvæ, while, in the rabbit, observations were made upon the response of the vascular endothelium to heat, pressure and slight injuries.

In preceding descriptions of living bloodvessels, the lability of the vascular system in respect to its growth capacity was emphasized since it was shown that the formation of new capillary networks and the remodeling of the vascular pattern characteristic of embryonic growth and wound healing are processes which occur constantly in the adult mammal in response to minute mechanical, chemical and thermal stimuli. The present observations have demonstrated the lability of vascular endothelium in respect to its consistency. It was found that endothelium may undergo a series of changes in consistency depending on the character and strength of the stimulus as follows:

Phase 1. Usual condition of normal circulating bloodvessels in which the lining is smooth and blood cells of all kinds slip along without sticking. Tonicity and elasticity present, also active contractility in amphibian vessels. (No definite endothelial contractility has been observed in rabbit capillaries.)

Pase 2. Slight change in consistency of endothelium in response to mild external or internal stimuli. Leukocytes stick to walls momentarily. This change is usually transitory but may persist for hours or days with no leukocyte emigration. It may suddenly revert at any time

to Phase 1. No impairment in tonicity or elasticity—or contractility (Amphibia).

Phase 3. Endothelium becomes more sticky—leukocytes cling more tightly to walls, in larger numbers. No impairment of tonicity or elasticity. This phase may be transitory and revert rapidly to Phase 2 or 1.

Phase 4. Further change of endothelium to apparently softer consistency. Leukocytes emigrate through walls. This stage is usually transitory—reversal to Phase 3 or 2 usually takes place after a few hours and may occur so abruptly as to snare leukocytes in walls. No evidence of endothelial injury.

Phase 5. Further change in endothelium of vessels subjected to mechanical injury or located near toxic substance (croton oil, infection). Loss of tonicity and elasticity—vessels collapsed if empty, or distended and distorted if they contain blood. Extravasation of erythrocytes at localized places in weakened endothelium, but no actual break in wall. Resumption of circulation in vessels in this phase causes irregular bulgings. Recovery from this phase to Phase 1 takes an appreciable time (several days).

Phase 6. Serious injury to endothelium with break in continuity of vessel wall which separates into solid hyalin globules which are ingested by macrophages. Retraction of endothelium at two ends of such a break. No recovery from this phase. In succeeding days there may be new growth of capillary sprouts into such regions.

The rapidity with which changes in endothelial consistency may take place, and the relatively minute stimuli necessary to elicit the preliminary changes, together with their reversibility are of undoubted importance for an understanding of the physiological activity of blood-vessels.

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